AD _____

(2)

BEHAVIORAL TOLERANCE TO ANTICHOLINERGIC AGENTS

FINAL REPORT

MARC N. BRANCH, PH.D.

NOVEMBER 20, 1986

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3188

Department of Psychology
University of Florida
Gainesville, Florida 32611

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION University of Florida Department of Psychology 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Gainesville, Florida 32611	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION US Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD-83-C-3188
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62734A; PROJECT NO. 3M1-62734A875; TASK NO. AE; WORK UNIT ACCESSION NO. 432

11. TITLE (Include Security Classification)
Behavioral Tolerance to Anticholinergic Agents

12. PERSONAL AUTHOR(S)
Marc N. Branch, Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 15 Jul 83 TO 15 Feb 86	1986 Nov. 20	44

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Atropine, physostigmine, operant behavior, tolerance, avoidance, positive reinforcement, antagonism, squirrel monkey
06	15		
06	16		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Squirrel monkeys were studied under four procedures in which their operant responses were maintained by either positive reinforcement (food presentation) or negative reinforcement (avoidance of brief electric shocks). Each procedure was designed to allow within-subject determination of drug effects. Another design feature was that reductions in responding resulted in different degrees of reduction of reinforcement frequency. Administered acutely, atropine reduced frequency of responding in a dose-related fashion, with responding maintained by positive reinforcement being much more sensitive to this action of the drug. Otherwise, there was little evidence that the type of reinforcement schedule influenced the action of the drug. Combining injections of atropine with injections of physostigmine yielded some evidence that atropine could antagonize the effects of physostigmine. Repeated administration of atropine after sessions did not result in consistent effects across subjects or across procedures. In some cases tolerance was observed, but in others it was not. Repeated post-session injections also did not result in consistent modification of the way that
(cont on back)

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Mary Frances Bostian	22b. TELEPHONE (Include Area Code) 301-663-7325
	22c. OFFICE SYMBOL SGRD-RMI-S

19. Abstract (continued)

atropine interacted with physostigmine. Repeated pre-session injection of atropine also did not result in consistent effects across procedures or subjects, with effects ranging from tolerance to sensitization. The data collected indicate that, in squirrel monkeys, atropine's behavioral effects tend to be highly idiosyncratic and difficult to predict.

AD _____

BEHAVIORAL TOLERANCE TO ANTICHOLINERGIC AGENTS

FINAL REPORT

MARC N. BRANCH, PH.D.

NOVEMBER 20, 1986

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3188

Department of Psychology
University of Florida
Gainesville, Florida 32611

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985.

TABLE OF CONTENTS

A-1

Background

Atropine is a cholinergic blocking agent that is active at muscarinic receptor sites and is used, among its other uses, as an antidote for effects of acetylcholinesterase inhibitors (1). The drug has a variety of behavioral and electrophysiological effects (c.f. 2,3). Acute effects have been studied with a wide variety of experimental preparations, including schedule-controlled behavior. Schedule-controlled behavior (behavior controlled by schedules of consequence presentation) is used for a variety of reasons. First, the procedures available allow for precise, reproducible control of behavior in individual subjects, thus obviating the need for averaging across several subjects for order to be observed. Second, such procedures yield behavior that is highly sensitive to the effects of drugs, including anticholinergics such as atropine (e.g., 4,5,6). Dosages that produce no overt, gross behavioral signs can have profound effects on schedule-controlled behavior (7), and, as McDonough (5) has recently noted, dosages that produce substantial effects on the schedule controlled behavior of non-human primates are comparable to those that produce significant changes in "cognitive" function in humans. Third, such procedures are related conceptually (and practically) to activities in everyday human behavioral functioning.

Schedule-controlled behavior is maintained performance; i.e., the new behavior being studied has already been acquired. Most of our everyday behavior is of this sort. We spend most of our time not learning new things but doing things we already know how to do. Thus, schedule-controlled behavior models much of our day-to-day activity. Also, schedule-controlled behavior is a result of a history of consequences. There can be no doubt that much human behavior also is influenced by its consequences, so schedule-controlled behavior accurately models human behavior in this regard, too. That schedule-controlled behavior provides a good model is attested to by the role that arranging consequences for behavior now has both in dealing with deviant behavior (see, for example, 8) and in education (see, for example, 9). These changes for the betterment of society have come as a direct outgrowth of laboratory research on the schedule-controlled behavior of non-humans.

Schedule-controlled behavior has been employed to assay the effects of atropine and other anticholinergic drugs. The effects that atropine has on schedule-controlled behavior (like those of many other types of drugs) depend on precisely how consequences are scheduled. Schedules that engender relatively constant rates of behavior usually result in atropine's producing progressively larger decreases in responding as the dose of the drug is increased (4,10,11,12). In contrast, when schedules produce temporal discriminations characterized by periods during which the response of interest is not made, increases in responding can be obtained (2,13,14).

Consequences that are arranged to produce schedule-controlled behavior can be divided into two major classes--positive and negative reinforcers (cf. 15,16). Positive reinforcers maintain behavior via presentation as a consequence of behavior, whereas negative reinforcers maintain behavior via removal or prevention of some event as a consequence of a response. The type of consequence maintaining behavior has been shown to be an important determinant of the behavioral action of drugs (e.g., 17,18,19), and there is evidence that type of consequence may

influence the actions of anticholinergics. For example, Herrnstein (20) found that scopolamine produced only dose-related decreases in responding maintained by food presentation (positive reinforcement) but that intermediate doses resulted in increases in responding that prevented electric shock presentation (negative reinforcement). The results are difficult to interpret unequivocally, however, because rates and patterns of responding under the two types of reinforcement were considerably different. Since drug effects may depend on differences in rates and patterns when the same reinforcer is used, it is important when comparing types of consequences to ensure that similar patterns of behavior are maintained by the different types of consequences (cf. 21). The research here yielded as one of its offshoots information regarding atropine's effects on behavior maintained by positive or negative reinforcement under circumstances in which the two types of consequences were presented according to comparable schedules so that equivalent performances were established and maintained.

Effects of chronic administration of atropine have not been studied extensively. This is especially true of behavioral effects. The research that has been conducted has been focused mainly on changes in muscarinic receptor sites that may occur as a consequence of repeated administration of large doses. For example, Herman and Slominska-Zurek (22) administered atropine (5.0 mg/kg) once per day to rats for 14 or 31 consecutive days. Intracerebroventricular injection of acetylcholine (10.0 ug) produced larger behavioral effects in chronically treated animals than in controls. The authors speculate that the changes were due to hypersensitivity of muscarinic receptor sites that developed because of the chronic blockade by atropine. This supposition is supported by the work of Takeyasu et al. (23), who determined, by means of direct receptor binding techniques, that chronic atropine (6.0 mg/kg/day for 4 weeks) resulted in an increased number of muscarinic receptor sites in rat brain. Takeyasu et al. (23) also reported modest tolerance to the activity-increasing effects (cf. 24) of 10.0 and 20.0 mg/kg of atropine in chronically treated subjects. Effects of chronic atropine administration on schedule-controlled performances have yet to be studied.

When drugs are administered repeatedly to subjects emitting schedule-controlled behavior, the phenomenon of behavioral tolerance may be observed. As Dews (25) has emphasized, behavioral tolerance should not be confused with simple tolerance as manifested in behavioral measures. Behavioral tolerance refers to changes in behavior following chronic drug administration that depend on the influence of behavioral factors for their occurrence. That is, behavioral tolerance will not result simply from repeated exposure to a drug, but instead depends upon both repeated drug administration and the operation of certain behavioral factors. A standard techique for demonstrating that tolerance has a behavioral component (cf. 26) is to compare the effects of repeated pre-test (a behavioral test session) drug administrations to those of an equal number of post-test administrations. The logic of such a comparison is that pre-test administrations allow the subject to engage in the measured behavior while drugged, during which time some sort of behavioral compensation may develop (i.e., the subject may "learn" to respond appropriately while in a drugged state). Post-test administrations, in contrast, result in the same amount of exposure to the drug but do not allow the subject to engage in the task while under the drug's influence. If tolerance is observed following pre-test but not post-test drugging,

the tolerance is said to be behavioral; if tolerance is greater for the pre-test condition than for the post-test condition, the tolerance can be called "behaviorally augmented" (27). Typically in such experiments two groups of subjects are used; one is exposed to a series of pre-test administrations and the other to an equal number of post-test administrations, and then the two groups are compared. Using this general method, behavioral tolerance has been observed for a variety of drug classes, including amphetamines (28,29,30), ethanol (26,31,32), hallucinogens (33), barbiturates (34,35,36), cocaine (37,38) and -tetrahydrocannabinol (39,40). Recently the method has been extended to a within-subject design (34). By studying first the effects of post-test drugging and then the effects of pre-test drugging, it is possible to demonstrate behavioral tolerance in a single subject.

All the experiments employed within-subject designs. Such designs are more "powerful" from a statistical point of view because the effects of variables can be assessed independently of between-subject differences. In addition, within-subject designs provide for a direct assessment of between-subject generality that is not provided by group means. Thus the research findings reported here are intended to be applicable eventually to individual subjects rather than to population characteristics. Finally, because the designs used include a great deal of replication within each subject, a direct assessment of the reliability of effects can be made. A detailed treatment of the benefits of within-subject designs is provided by Sidman (41).

The major hypothesis concerning the kinds of factors that make behavioral tolerance likely to be observed is the "cost" or "reinforcement loss" hypothesis (42,43). As originally stated, the hypothesis is that behavioral tolerance is likely to be observed "where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcement." (43, p. 181) That is, if a drug's effect is to reduce the frequency of reinforcement (either positive or negative) during a test session, repeated pre-test drugging is likely to result in tolerance development. The subject "compensates" in some way so that the frequency of reinforcement returns to its original level. A corollary of the hypothesis is that drug-induced changes in behavior that do not reduce reinforcement frequency will not diminish (i.e., show tolerance) with repeated pre-test administration.

Although biochemical data are lacking on this point, behavioral tolerance (i.e., an adjustment that restores or tends to restore reinforcement frequency to pre-drug levels) may occur independently of any changes in drug-receptor interactions. That is, behavioral tolerance may occur even though other mechanisms of tolerance (e.g., receptor affinity changes, receptor number changes) are not involved. The experiments described here were designed to test this hypothesis, albeit somewhat indirectly. The specific goals of the work reported here include the following:

1.) To delineate acute effects of atropine on schedule-controlled behavior and examine atropine's ability to antagonize behavioral effects of the reversible cholinesterase inhibitor physostigmine. Physostigmine was used because it is centrally active and its effects are reversible (1).

2.) In all procedures to compare effects of pre-test dosing with those of post-test dosing to determine to what extent tolerance was behavioral in nature. Changes in atropine's ability to antagonize physostigmine were also examined as a function of pre- or post-test dosing with atropine. It was predicted that behavioral tolerance would develop in the absence of changes in atropine's ability to block cholinesterase inhibitors.

3.) To compare effects of acute and chronic atropine on behavior controlled by positive versus negative reinforcement. Procedures were employed that resulted in equivalent rates and temporal patterns of responding under the two types of maintaining conditions. Also determined was whether positive or negative reinforcement influences atropine's ability to antagonize physostigmine.

4.) To compare atropine's chronic effects on responding maintained by positive reinforcement or by negative reinforcement in circumstances in which drug-induced changes in behavior either led to decreased reinforcement frequency (i.e., to some "cost") or did not.

5.) To ascertain, in situations in which either the probability or the frequency of reinforcement was equated, whether "reinforcement loss" determined that behavioral tolerance to atropine had occurred.

Methods

General Considerations. Adult, male squirrel monkeys (Saimiri sciureus) were subjects under all procedures. Subjects numbered 531-536 were experimentally naive, whereas those with lower numbers had been exposed previously to schedules of positive and negative reinforcement and to other drugs. None of these subjects had received drugs for more than a year before the beginning of the present experiments. Monkeys were studied in restraining chairs equipped with levers, food-pellet dispensers, stimulus lights, and tail stocks as needed. The chairs provided for restraint via a waistlock that allowed for free movement of the entire upper body while the monkey was seated in a comfortable position. Tail stocks held a shaved portion of a monkey's tail motionless when electric shocks were delivered.

Monkeys were maintained at about 85% of their free-feeding weights. Under schedules of food presentation (see below for more detail), monkeys received individual 190-mg, banana-flavored food pellets (P. J. Noyes Co.). Electric shocks were delivered via two brass electrodes that rested on a shaved portion near the end of a monkey's tail. The tail was treated with electrode paste (EKG Sol) to ensure consistent resistance. Shocks were 100 msec in duration and ranged from 1.0 to 5.0 mA. Intensity was fixed in each procedure. Shocks within this range are harmless.

The behavioral procedures used in this project all involved multiple schedules. A brief description of the general features of multiple schedules may help make the subsequent detailed descriptions clearer. Multiple schedules are arranged so that different stimulus conditions "signal" when different procedures are in effect. Their use allows more than one procedure to be studied in a single subject virtually at the same time. Differing performances essentially are "on call" by the experimenter, who can produce any of a number of behavioral processes merely by changing stimuli. Typically, the different stimuli and

contingencies (together called a component) alternate through daily test sessions.

Experimental events were arranged and data collected by a digital minicomputer (PDP8/F) operating under the SuperSKED software system (44). During test sessions restraining chairs were housed in sound- and light-attenuating enclosures that were located in a room adjacent to the one housing the computer. White masking noise was continuously present in the testing room. Cumulative response records were made during each test session to provide continuous visual monitoring and a continuous record of performance in each session. In addition, a low-light video camera and monitor were used to observe monkeys during tests.

Drug Procedures. Drugs used were atropine sulfate (provided by U.S. Army Medical Research and Development Command) and physostigmine salicylate (Sigma). They were diluted in distilled water and injected intramuscularly (i.e., into the thigh muscle; opposite thighs when two injections were made) in a volume of 0.5 ml/kg body weight. Injections were made 10 min before a test session. Once performance had stabilized under a particular behavioral procedure (see below for detailed descriptions) a series of pharmacological manipulations was made. First, acute effects of atropine alone were determined across a range of doses. Drug administrations were spaced by at least 5 days, whereas behavioral testing occurred daily so that it could be determined whether atropine's effects carried over from the day of injection. Doses were administered in two ascending series initially. Following this, additional doses were sometimes tested in an irregular order. Following determination of dose-effect curves for atropine, the effects of the same doses of atropine were studied in combination with physostigmine, so that antagonistic effects of atropine could be assessed. The dose of physostigmine studied varied across subjects. Usually a response-rate-reducing dose was studied. However, in some subjects, the smallest dose to produce rate reductions produced substantial overt signs (e.g., excessive salivation). In those cases a slightly smaller dose was studied.

Next, effects of administering the drug repeatedly were assessed. A response-rate-lowering dose was chosen to be given repeatedly. During these tests, sessions were conducted and injections were made once every other day because more frequent drugging would have jeopardized the animals' health. Specifically, the doses of atropine that were given repeatedly often would suppress or abolish eating for nearly a day. Daily administration, then, might have resulted in starvation. Initially, a fixed dose of atropine was administered approximately 30 min after each session, with each session being preceded by a sham (needle puncture) injection. Following the first 10 such injections, sessions occasionally were preceded by injections of atropine. These "probe" injections were made no more often than once every five sessions and were made to examine the dose effects of atropine during repeated post-session administration of the drug. Probe doses were given in two ascending series, and probe sessions were followed by a sham injection rather than the usual daily dose.

Following the determination of atropine's effects during repeated post-session drugging, the effects of atropine in combination with physostigmine (still during the same regimen) were measured. Combinations of atropine with the same dose that had been used during acute

determinations were injected as probes before selected sessions. These tests allowed us to determine whether the nature of the interaction between atropine and physostigmine had been altered during repeated post-session administration of atropine.

The repeated post-session drugging phase was followed immediately by a phase in which atropine was administered before each session (with a sham injection occurring about 30 min after each session). Sessions continued to be conducted every other day. After the first ten sessions of this phase, doses other than the regularly administered one occasionally were substituted, again as probes, so the dose-effects of atropine could be determined. As before, probes were administered in two ascending series with at least five "normal" sessions intervening between successive probes. In those cases for which it was appropriate, the determinaion of dose effects of atropine during repeated pre-session drugging was followed by an assessment of the interaction between atropine and the dose of physostigmine used earlier. That is, the full range of atropine doses were administered in combination with the selected dose of physostigmine. These injections were made before selected sessions, and each combination was tested twice.

Behavioral Procedures. Four behavioral baselines were studied. Among them they allowed for comparisons along three dimensions: (a) between two major classes of consequences, positive and negative reinforcement; (b) between disruptions of behavior resulting in substantial and minimal reinforcement loss; and (c) between cases in which response rates under different maintaining circumstances were and were not similar. Since previous work with other drugs (and in some cases with atropine itself) had shown that these factors (type of consequence, reinforcement loss, and baseline rates) can be important, their inclusion in the project allowed for results and conclusions that have added generality. All procedures were arranged so that the maximum session length was about 1 hour. Atropine's duration of action in squirrel monkeys is substantially longer than that (4). In addition, the behavioral effects of physostigmine, at the doses tested, persisted for at least 1 hour.

Procedure 1: Comparable performances maintained by interval schedules of positive versus negative reinforcement. In this procedure, monkeys were trained to press a lever under a two-component multiple schedule. The schedule in one component was a variable-interval (VI) 60-s schedule of food presentation. The schedule in the other component was a VI 15-s avoidance procedure similar to that employed by deVilliers (45). Under this schedule, brief, inescapable 4-mA electric shocks were scheduled at random intervals averaging 15 s. A response prior to the next scheduled shock cancelled that shock, and so on. Both the VI schedule of food presentation and the VI avoidance schedule resulted in steady rates of responding that generally were slightly higher under the avoidance schedule (See Figure 1). Components were cued by colored lights and were 10 min in duration. Sessions lasted 60 min and the component in effect at the beginning of the session was determined randomly. Data (rates of responding, food presentations, shocks, inter-response time distributions) were collected over 20-min blocks so that the time course of drug action could be monitored. Ninety-two, 99 and 93 sessions were needed to establish stable performance for monkeys 524, 531, and 532, respectively.

This procedure allowed examination of atropine's effects on comparable performances that were controlled by different types of consequent events. Also, because of the interval schedules used, substantial drug-induced changes in behavior could have relatively little effect on the frequency of food delivery or shock delivery.

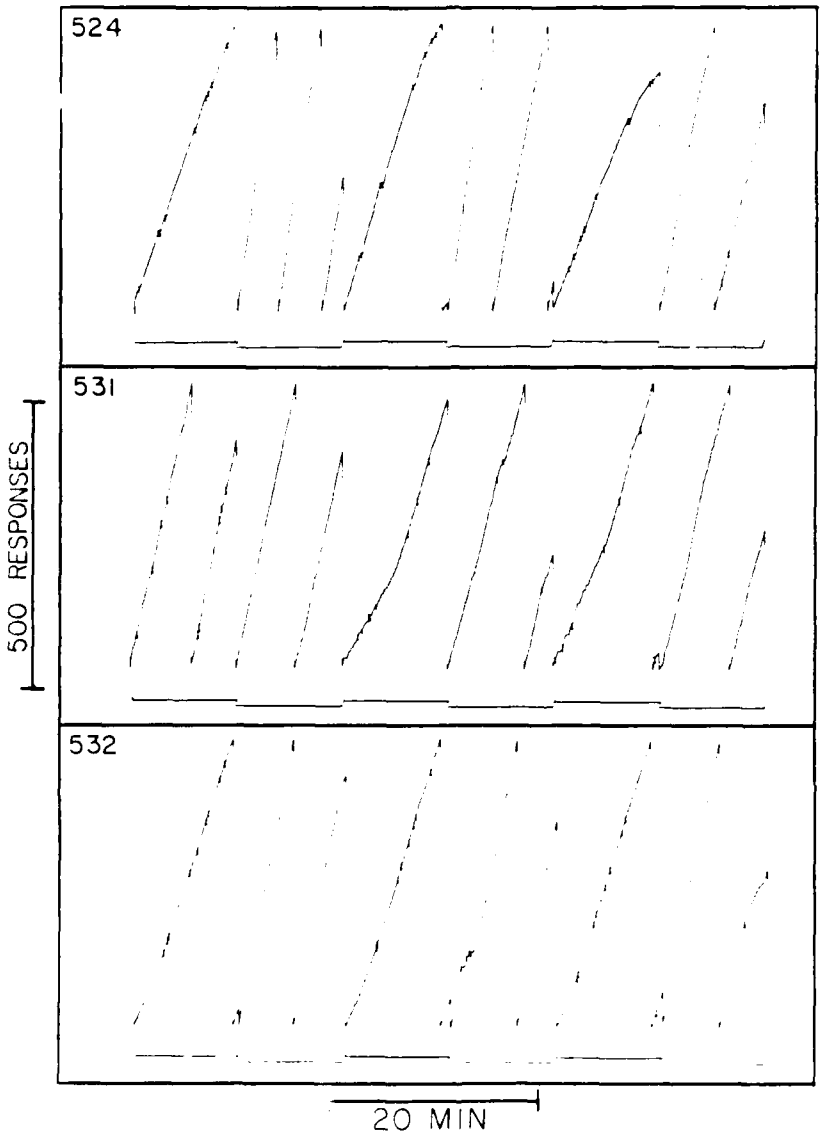

Figure 1. Cumulative records from three squirrel monkeys on a multiple variable-interval 60-s food reinforcement (bottom pen up)/variable-interval 15-s shock deletion schedule (bottom pen down). Upper-pen deflections indicate shock or food delivery.

Atropine produced dose-related decreases in response rate for all three subjects. As noted in Figure 2, responding under the VI schedule of food reinforcement decreased at smaller doses than did responding under the avoidance schedule. It is interesting that the monkeys did not eat all the food pellets they earned when drugged.

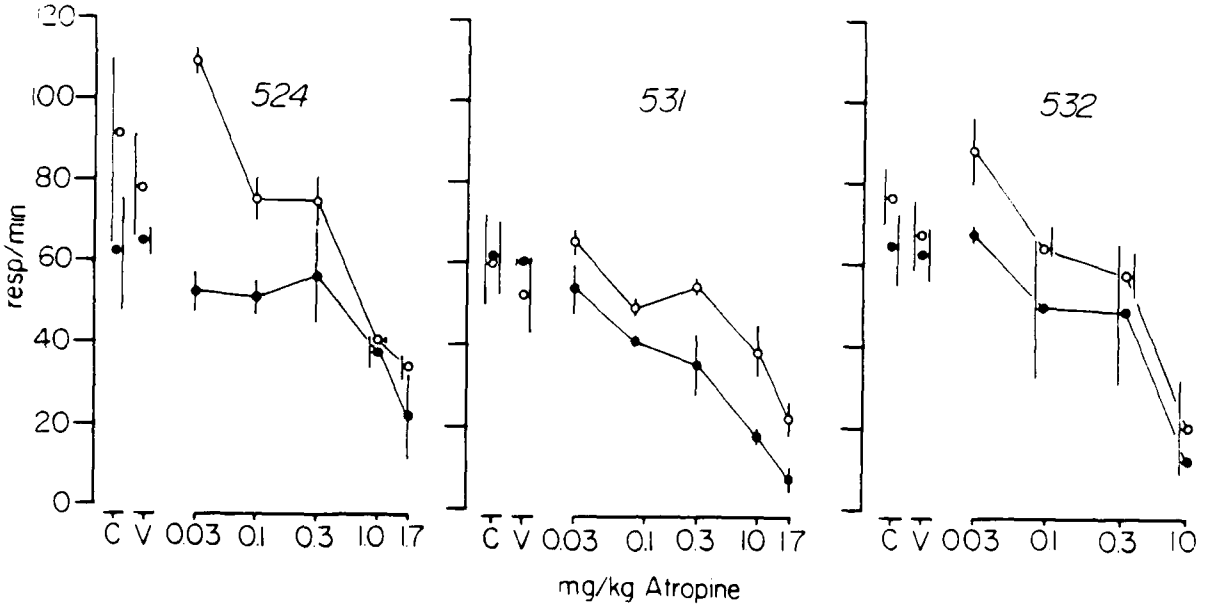

Figure 2. Dose-effect curves for three squirrel monkeys across a range of atropine doses. Open circles indicate mean response rates in the shock-deletion component of the multiple schedule; filled circles indicate mean response rates in the food reinforcement component. Rates for vehicle (sterile water) injections are shown over the V. Each atropine dose was administered twice, as was the vehicle. Points above C are means from all sessions that occurred the day before a drug or vehicle test.

Figure 3 shows the relation between dose of atropine and percentage of earned pellets eaten. At the larger doses, virtually no pellets were eaten, although many were earned. Monkey 531 was especially sensitive to the appetite-suppressing effects of the drug, although the sensitivity appeared taste- or texture-specific. Specifically, following administration of doses of 1.0 or 1.7 mg/kg, this monkey refused food pellets and monkey chow for up to 3 days. He accepted fruit and peanuts, however.

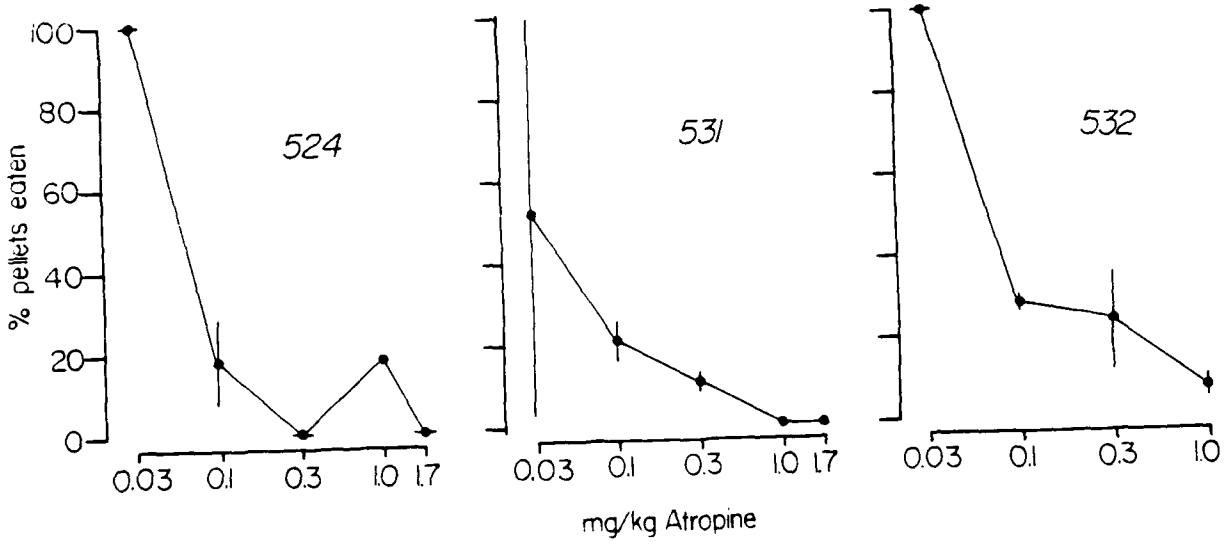

Figure 3. Percent of delivered food pellets eaten by three squirrel monkeys across a range of atropine doses. Vertical lines indicate the range of percent of pellets eaten. Each dose was administered twice. One hundred percent of the food pellets were eaten under control and vehicle injection conditions.

The dose-effect curve for atropine also was determined in the presence of 0.08 mg/kg of physostigmine for these subjects, and the resulting data are presented in Figure 4. Some evidence of antagonism is present (compare with Figure 2) in these curves, but the effects are not great. Testing for carry-over effects revealed no measurable antagonism after 24 hours.

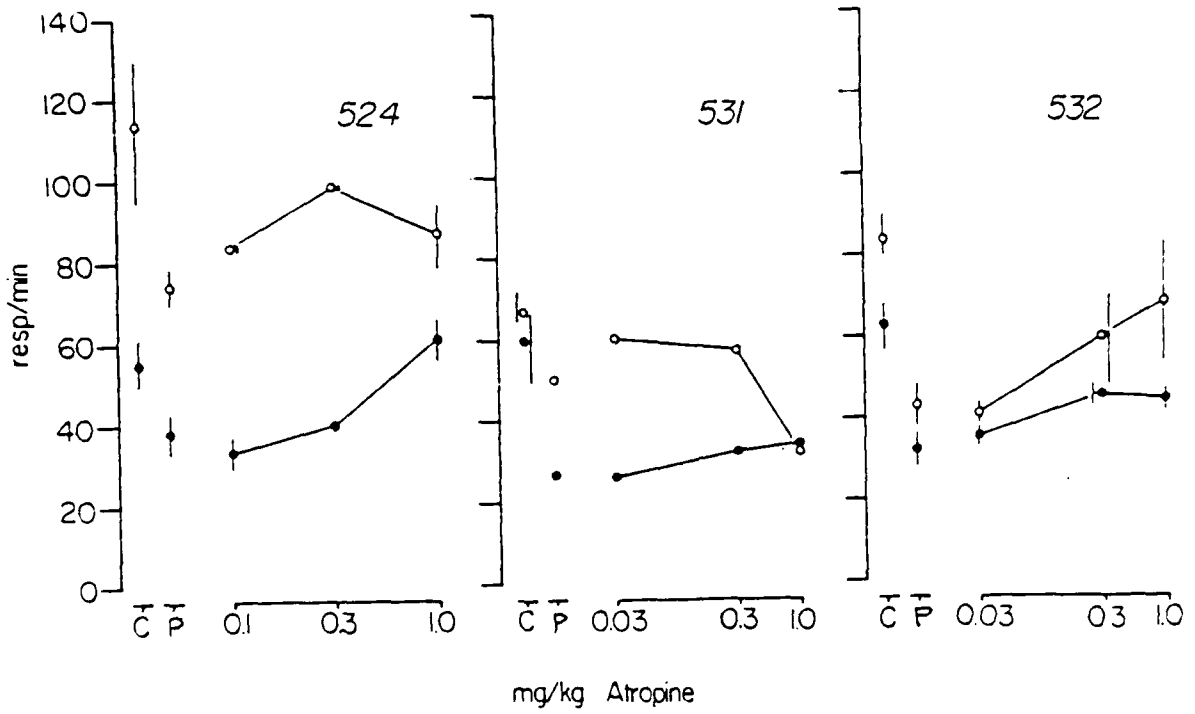

Figure 4. Dose-effect curves for three squirrel monkeys across a range of atropine doses combined with 0.08 mg/kg physostigmine. Open circles indicate mean response rates in the shock-deletion component of the multiple schedules; filled circles indicate mean response rates in the food-reinforcement component. Vertical lines indicate the range of response rates. Response rates for control conditions are shown over C; rates for vehicle (sterile water plus physostigmine injections) are shown over P. Each atropine/physostigmine dose was administered twice for monkeys 524 and 532, and once for monkey 531.

Figures 5 and 6 display the effects of atropine during repeated administration of 1.0 mg/kg after sessions and during the phase where the dose was administered prior to each session. Effects of acute administrations are also shown to aid in comparisons.

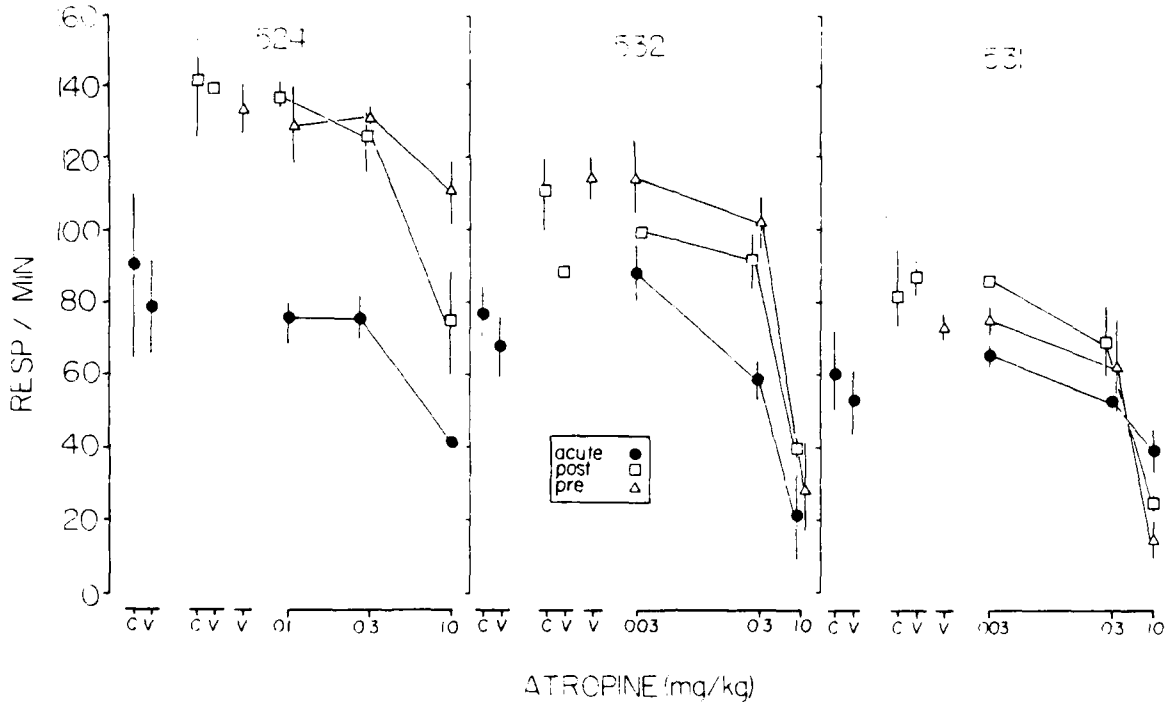

Figure 5. Effects of atropine on responding maintained by a schedule of electric shock deletion. All points are means of at least two determinations. Bars indicate ranges. Filled circles indicate acute effects; open squares indicate effects during repeated (every other day) injection of 1.0 mg/kg of atropine after each session; open triangles show effects when 1.0 mg/kg of atropine was administered before each session. Points above C indicate means for control sessions. Points above V show effects of the vehicle.

Figure 5 shows data from the variable-interval shock avoidance condition. For all three subjects, baseline lever-pressing rates were higher during the phases when atropine was administered repeatedly. There was no evidence of the development of tolerance during either pre-session or post-session administration of atropine. In fact, on a proportional basis, the data for Monkeys 532 and 531 indicate an increased sensitivity to the effects of 1.0 mg/kg during both types of chronic drugging. Figure 6 displays effects of atropine on responding during the variable interval schedule of food presentation. Here there was some evidence of tolerance. For Monkey 524 the effects of 1.0 mg/kg were diminished during both chronic pre- and post-session drugging, and the effects of 0.3 mg/kg were reduced for Monkey 532 duing both chronic regimens. It is important to note, however, that even though effects on response rates were attenuated, the monkeys did not eat any of the earned pellets at doses of 0.3 mg/kg or greater.

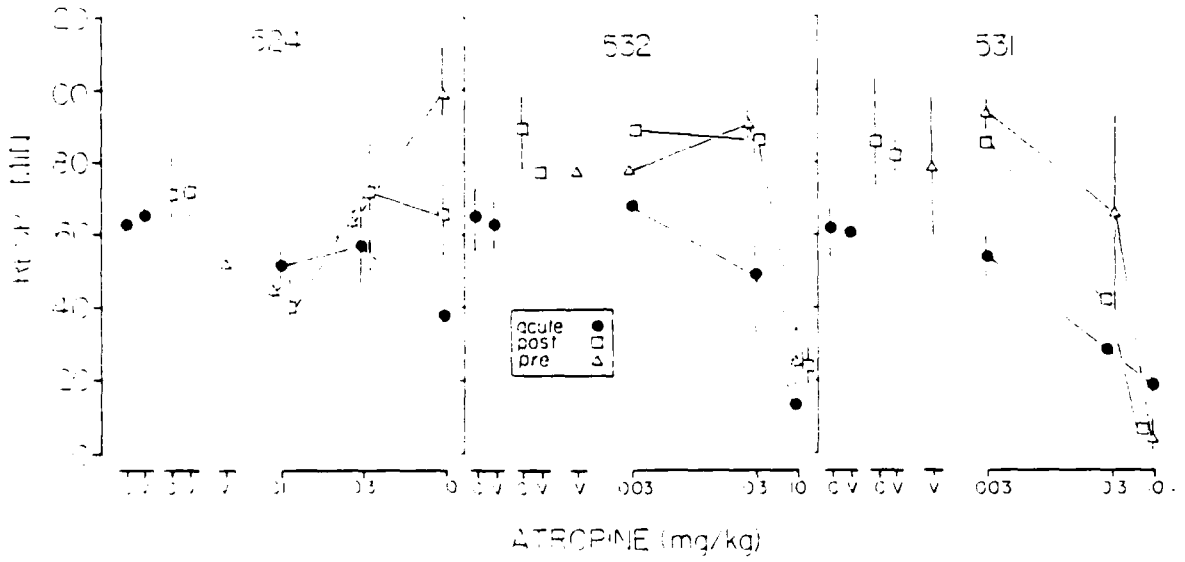

Figure 6. Effects of atropine on responding maintained by a variable-interval schedule of food presentation. Details are the same as for Figure 5.

Effects of atropine in the presence of 0.08 mg/kg of physostigmine are shown in Figures 7 and 8. Figure 7 depicts effects during the schedule of shock avoidance. Subject 531 was not exposed to combinations of atropine and physostigmine during the repeated pre-session drugging phase. For Subject 524, chronic administration of atropine altered the way in which the drug interacted with physostigmine; substantial increases in response rate were seen when the two drugs were combined.

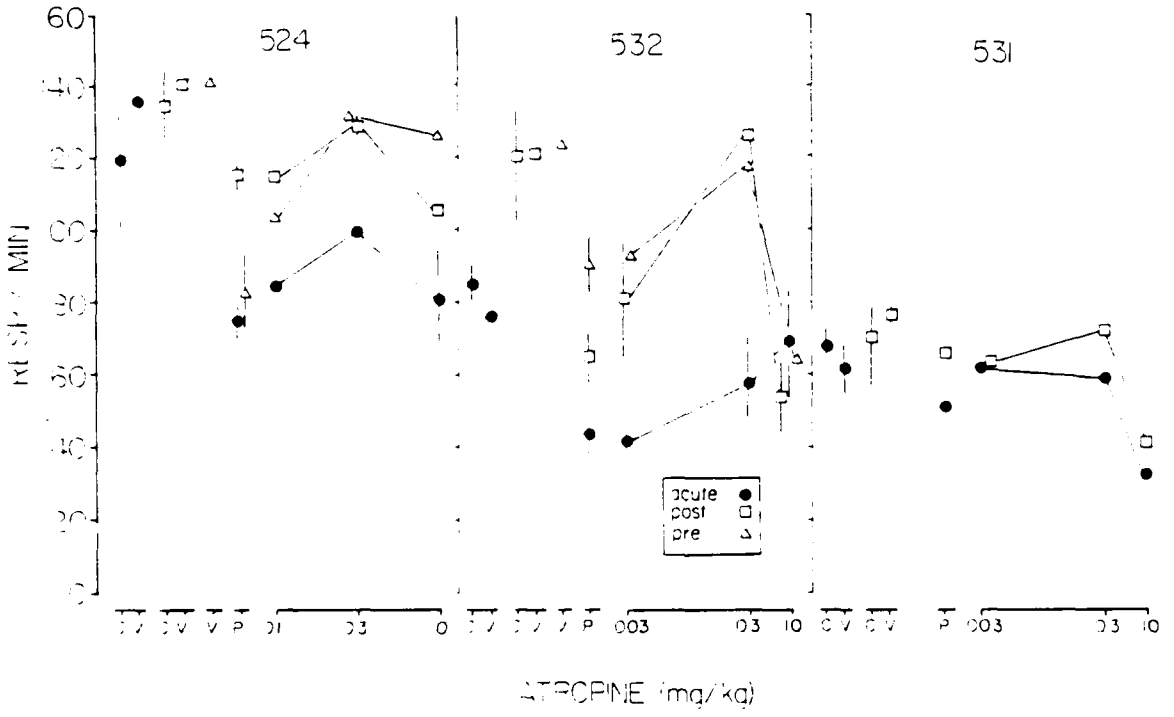

Figure 7. Effects of atropine in combination with 0.08 mg/kg of physostigmine on responding maintained by a variable interval schedule of shock deletion. Points above P show effects of 0.08 mg/kg of physostigmine alone. Other details are the same as for Figure 5.

These increases were largest when atropine was administered before each session. For Monkey 532, repeated atropine administration resulted in an enhancement of atropine's ability to antagonize the response rate-decreasing effects of physostigmine. No such effect was seen in Subject 531's performance, however, when combinations of atropine and physostigmine were studied while atropine was being administered after each session. Figure 8 illustrates the effects of combinations of atropine and physostigmine on responding under the variable-interval schedule of food presentation. As was the case for responding maintained by shock avoidance, repeated atropine administration altered the way the drug interacted for Monkeys 524 and 532. The dose of 0.3 mg/kg was more effective as an antagonist of physostigmine's effects during repeated administration of atropine.

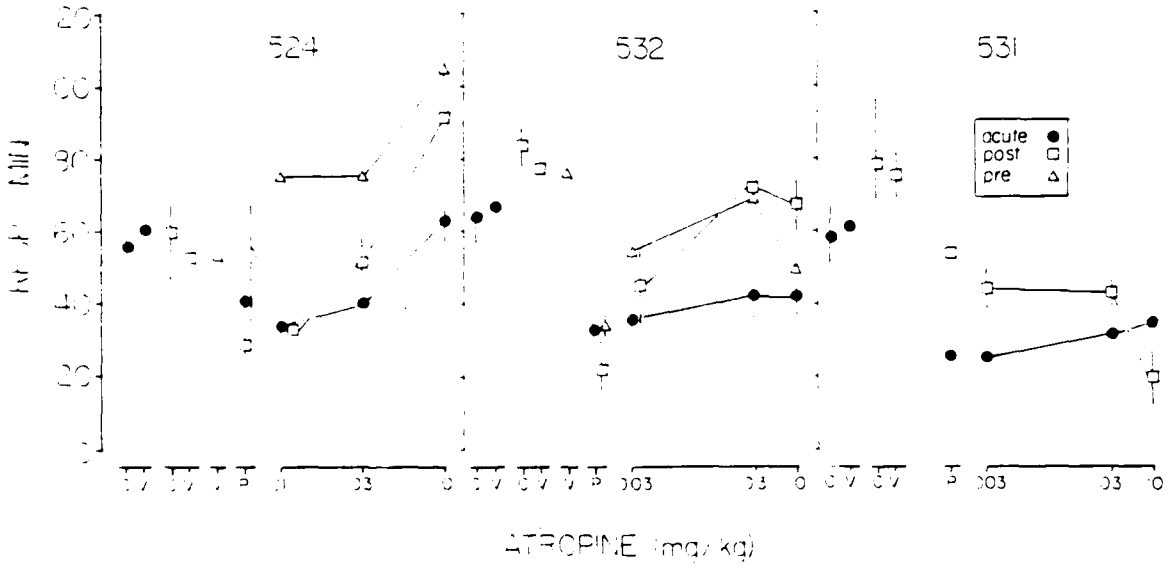

Figure 8. Effects of atropine in combination with 0.08 mg/kg of physostigmine on responding maintained by a variable interval schedule of food presentation. Details are the same as those in Figure 7.

Procedure 2: Comparable performances maintained by ratio schedules of positive versus negative reinforcement. A two-component multiple schedule was employed with a fixed ratio (FR) schedule of food presentation in one component. For two monkeys the schedule was FR50 and for the third, FR35. In the other component, an equal-value FR schedule of termination of a shock-stimulus complex was programmed. Under this procedure, completing the schedule resulted in a 30-s time-out period (all lights in the experimental enclosure were extinguished and responses had no programmed consequences). Failure to complete the schedule within a specified time limit (62 s for FR50 and 47 s for FR35) resulted in the initiation of brief, inescapable electric shocks at 3-s intervals until the response requirement was satisfied, or until five shocks had been

delivered. Each food presentation under the FR50 schedule in the other component also was followed by a 30-s time-out period. Components alternated irregularly after each time-out period, with the restrictions that the maximum number of successive occurrences of one component was five and that an equal number (30) of each type of component occurred in each session. A time limit was also in effect during components scheduled to end with food presentation. The time limits on the two components guaranteed exposure to both of them in the event that responding was suppressed selectively in one or the other. Data recorded included overall response rates, pre-ratio pause duration, running rates (rate computed exclusive of pre-ratio pause time), shocks received, food deliveries, and time-limit expirations. One hundred sixteen, 117, and 99 sessions were needed to establish stable performance in Monkeys 523, 525, and 535, respectively.

Figure 9 shows cumulative records of responding under non-drug conditions for the three monkeys in the study. Comparable rates and temporal patterns were controlled by the two different consequences.

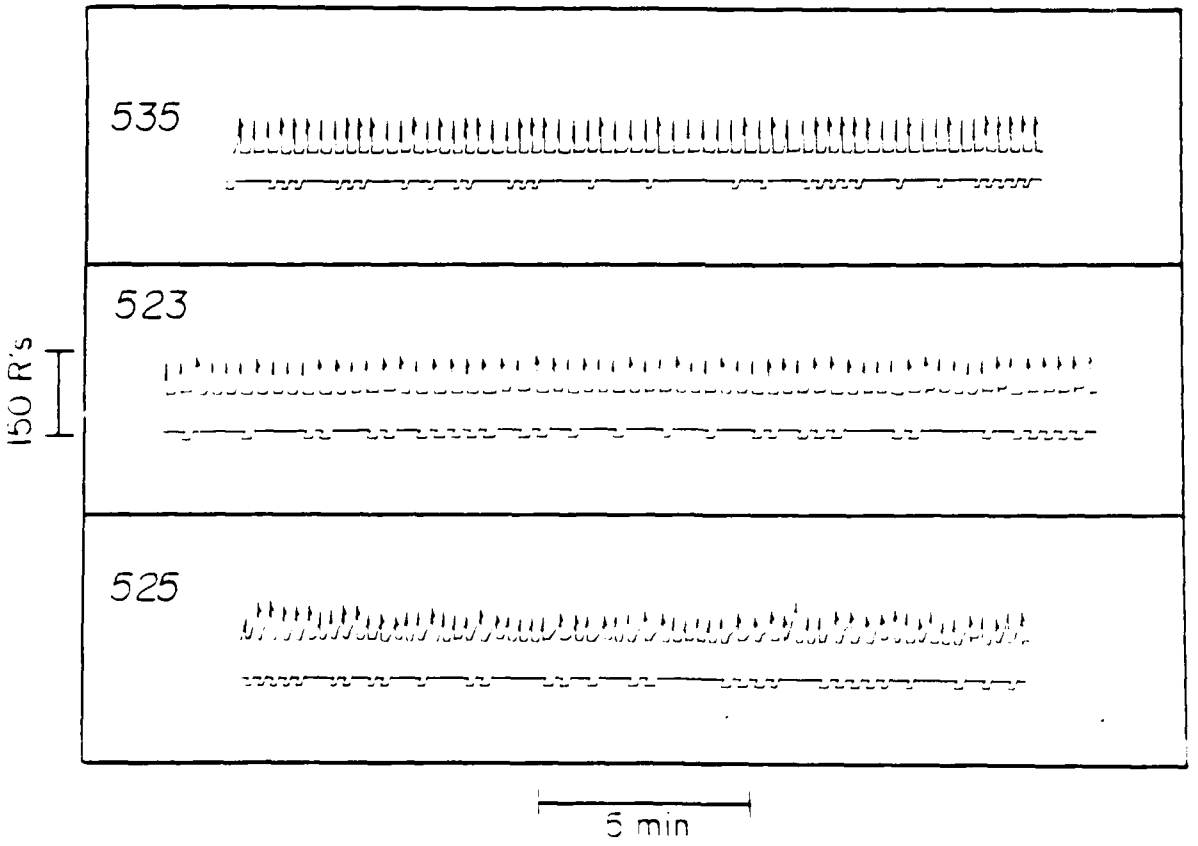

Figure 9. Cumulative records of lever pressing under the multiple fixed-ratio (food presentation) fixed-ratio (termination of shock-associated stimulus) schedule.. Schedules were FR50, FR50, and FR35 for monkeys 535, 523, and 525, respectively. Y-axis: cumulative responses; X-axis: time. The event pen was deflected when the food-reinforcement schedule was in effect, and the stepping pen was reset to the baseline at the end of each ratio. Hatch marks denote food pellet presentations or shocks. The recorders functioned during the 30-s time-out periods that followed each ratio.

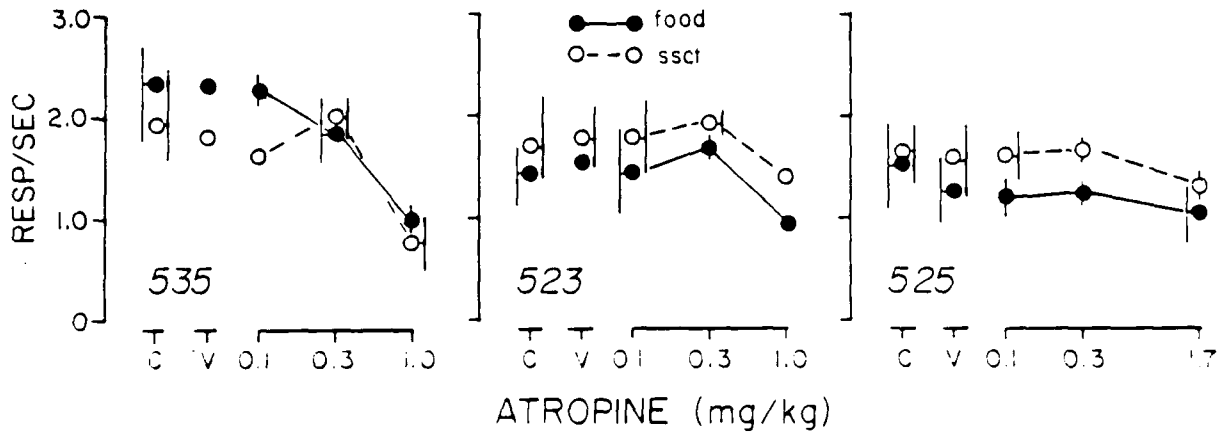

Figure 10. Response rates as a function of dose of atropine. Filled circles show data from food-reinforced responding and open circles, those from the schedule of shock-stimulus-complex termination. Points above C are means from all control sessions (those that preceded drug tests), and those above V show effects of administering the vehicle (water). Bars indicate ranges. Other details are as before.

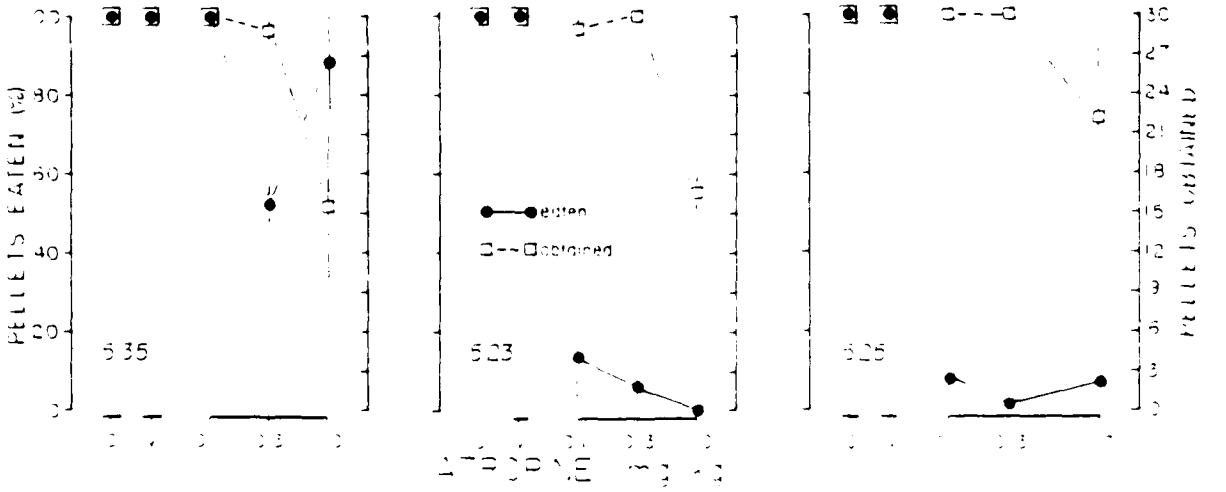

Figure 11. Number of food pellets earned and percentage eaten as a function of atropine dose. Filled circles show percentage of obtained pellets eaten (left Y-axis), and open squares show number of pellets obtained (right Y-axis). Points above C and V show effects during control sessions and those preceded by vehicle, respectively. Bars indicate ranges.

Dose-effect data for atropine on response rates are displayed in Figure 10. As in the previous study, only decreases in response rates were observed, with a tendency for responding under the schedule of positive reinforcement (i.e., food presentation) to be more sensitive. Also, monkeys in this study, like those described above, did not eat all the food pellets they earned. Although substantial decreases in rate were observed only in one subject (Monkey 535), it was our judgment that the larger doses were sufficient because the number of expirations of the time limit during the FR schedule of food reinforcement increased considerably (see Figure 11) and the monkeys received a significant number of shocks under the FR schedule of shock-stimulus-complex termination. Under control or vehicle conditions, the monkeys rarely received shocka Under the largest dose tested for each monkey, the mean numbers of shocks received were 11.5, 44, and 8.5 for Monkeys 535, 523, and 525, respectively. The dose-effect curves for pellets eaten are given in Figure 11. These subjects, too, failed to eat their rations of monkey chow on the day on which a large dose (e.g., 1.0 or 1.7 mg/kg) was administered, but they all ate normally by the next day.

Figure 12 displays the effects of atropine during the repeated post- and pre-session administration phases. Subject 525 was not exposed to chronic pre-session drugging. Subjects 523 and 535 were exposed to repeated administration of 1.0 mg/kg of atropine, whereas Monkey 525 was given 1.7 mg/kg as the chronic dose. Only the data for Monkey 535 display any evidence of tolerance. For this subject the effects of 1.0 mg/kg were attenuated during both food-reinforced and avoidance components of the schedule. As was the case for the subjects exposed to Procedure 1, none of these subjects ate any of the earned food pellets following administration of doses of atropine of 0.3 mg/kg or larger.

Shown in Figure 13 are effects of combinations of atropine and physostigmine. For Subjects 523 and 525 the dose of physostigmine was 0.08 mg/kg, whereas the dose for Monkey 535 was 0.16 mg/kg. The dose-effect curve for atropine was altered by physostigmine for all three subjects. The nature of these alterations can be seen by comparing the curves in Figure 13 to those in Figure 10. For Subject 523 the effects of atropine were diminished by concurrent administration of 0.08 mg/kg of physostigmine. This effect occurred under conditions of acute administration and during both repeated-drugging phases. That is, repeated atropine administration did not change the way that atropine and physostigmine interacted. For Subject 525, effects were similar to those observed in Monkey 523. Rate-decreasing effects of atropine were eliminated by concurrent physostigmine administration, and at higher doses of atropine the combination resulted in response rates that were above baseline. Repeated post-session adminstration of atropine did not change the effect. For Monkey 535, not only did physostigmine change the dose-effect curve for atropine, but repeated atropine adminstration also changed the nature of the interaction of the two drugs. Under acute conditions atropine antagonized the rate-decreasing effects of physostigmine in a dose-related fashion; larger doses of atropine were more effective antagonists. During repeated pre-session drugging with 1.0 mg/kg of atropine, however, the antagonistic efficacy of atropine was enhanced; i.e., small doses that had negligible effects as antagonists under acute conditions became effective antagonists under conditions of chronic administration. This, of course, is an effect that seems to illustrate increased sensitivity to atropine rather than tolerance.

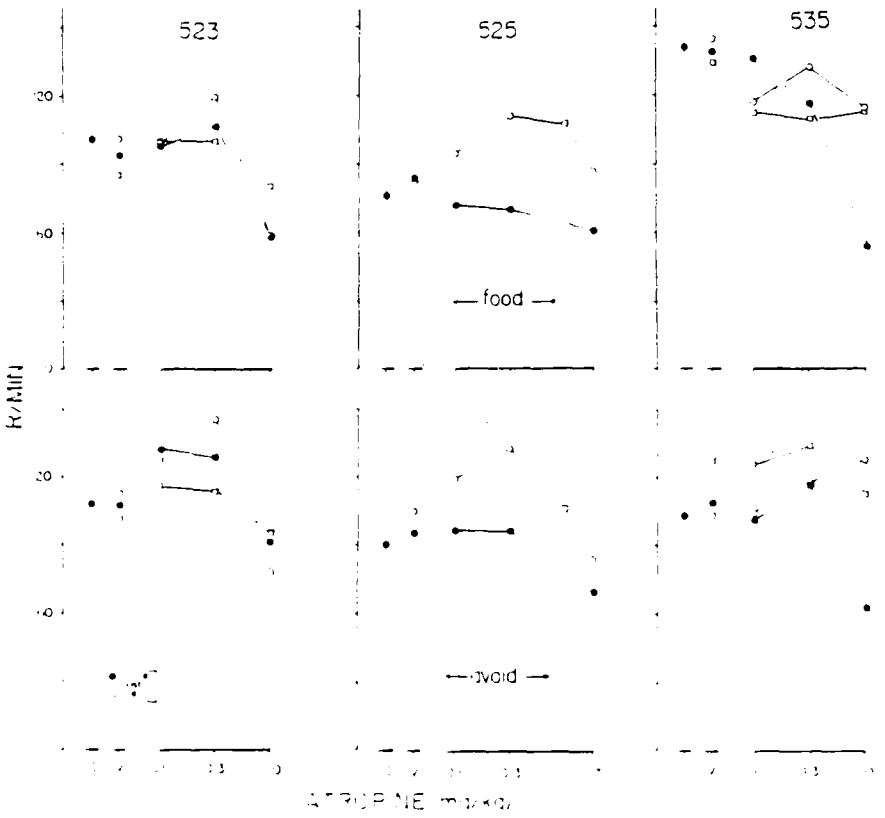

Figure 12. Response rates as a function of atropine dose during acute administration (filled circles), during repeated post-session drugging (open circles), and during repeated pre-session drugging (open squares). The top row of graphs show data from the fixed-ratio schedule of food presentation and those in the lower row show data from the fixed-ratio schedule of termination of a stimulus-shock complex. Points above C show means and ranges of control sessions during acute determinations. Points above V show effects of injecting the vehicle.

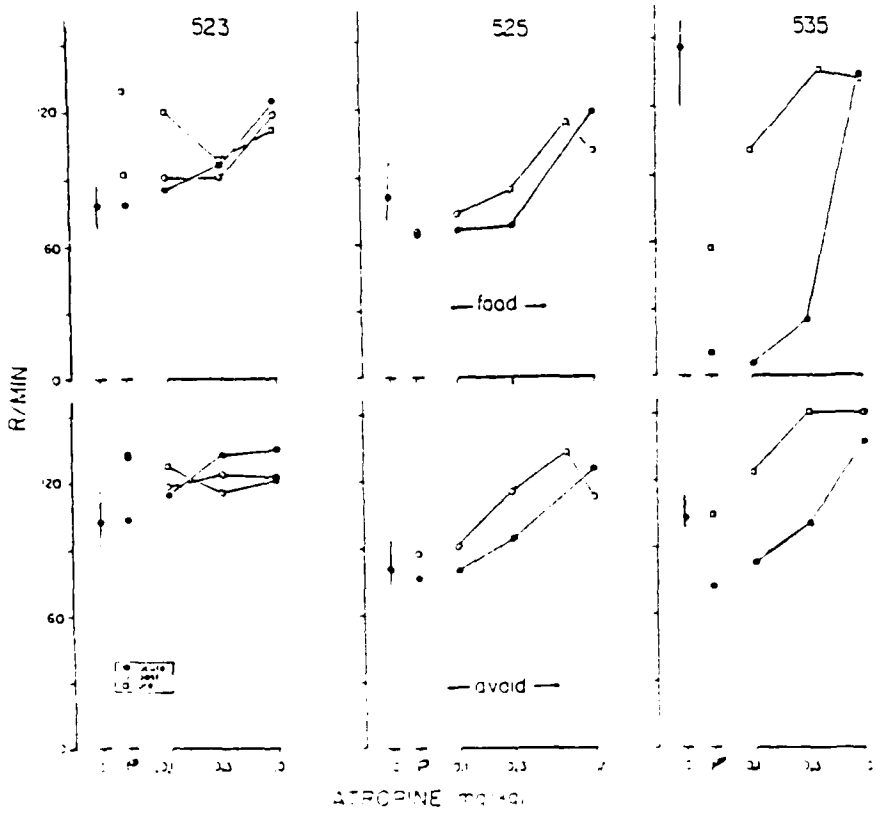

Figure 13. Response rates as a function of atropine dose in the present of physostigmine during acute (filled circles) and repeated (open circles) post-session dosing, and repeated pre-session drugging (open squares). Points above C show means and ranges of control values during acute administration. Points above P show effects of injecting the vehicle in combination with physostigmine. The doses of physostigmine were 0.08 mg/kg for Monkeys 523 and 525 and 0.16 mg/kg for Monkey 535.

Procedure 3: Performance under ratio and interval schedules of food presentation in which the probability of food presentation was equated. Lever pressing was established under a two-component multiple schedule of food presentation. In one component, a VI 60-s schedule of food presentation was used. While this component was in effect, the number of lever presses per food presentation was recorded. The other had a variable-ratio schedule. The numbers of responses required for each food presentation under this schedule were the same as those for the preceding VI component. That is, the VR schedule was "yoked" to the VI schedule so that the number of responses per food presentation and the distribution of these numbers were matched for the two components. Components alternated after two to seven food presentations. Five of each type of component occurred in each session. Because of the "yoking," each VR component lasted for the same number of food presentations as the immediately preceding VI component. Once stable performance was achieved, the "yoking" relationship was broken, and the VR schedule was fixed from that point. The VR values were taken from the median VR of the last 11 sessions in which yoking was in effect. Otherwise, details of the multiple schedule remained unchanged. Time limits employed for completion of components ensured that, in the case of total, or near total, suppression of lever pressing by drugs, exposure to each type of component would occur. The time limit for a VI component was 200% of the programmed inter-food presentation time for that component. The following VR component was limited to a programmed maximum time equal to the maximum allowed for the immediately preceding VI component. Monkey 512 required 152, Monkey 514 required 107, and Monkey 533 required 102 sessions of training to establish stable responding.

This procedure allowed for a within-subject analysis of drug-effects on VI and VR responding in a situation in which number of responses per reinforcement, and the distribution of those number over time were roughly equated. Under the ratio schedule, food-presentation frequency was directly related to lever-pressing rate, whereas under the interval schedule, food-presentation frequency was relatively independent of response rate (until extremely low rates occurred). Consequently, drug-induced rate decreases produced reinforcement loss in the VR component that was proportional to the response-rate decrease, but were less likely to result in reinforcement loss in the VI component.

Control performance under this procedure was characterized by constant rates of responding, with higher rates prevailing during the VR schedule. Typical control performance is illustrated in the cumulative records of Figure 14.

As with performance under the procedures already described only decreases in response rate were observed following administration of atropine. These are characterized in the data displayed in Figure 15. The range of effective doses was an order of magnitude less than the range employed for negative reinforcement procedures. That is, behavior motivated solely by food presentation was considerably more sensitive to atropine's effects than was behavior motivated by avoidance of electric shock. Atropine also suppressed eating of food pellets under this procedure. At the largest doses, none of the delivered pellets were consumed. These doses also abolished eating in the home cage for about 24 hours.

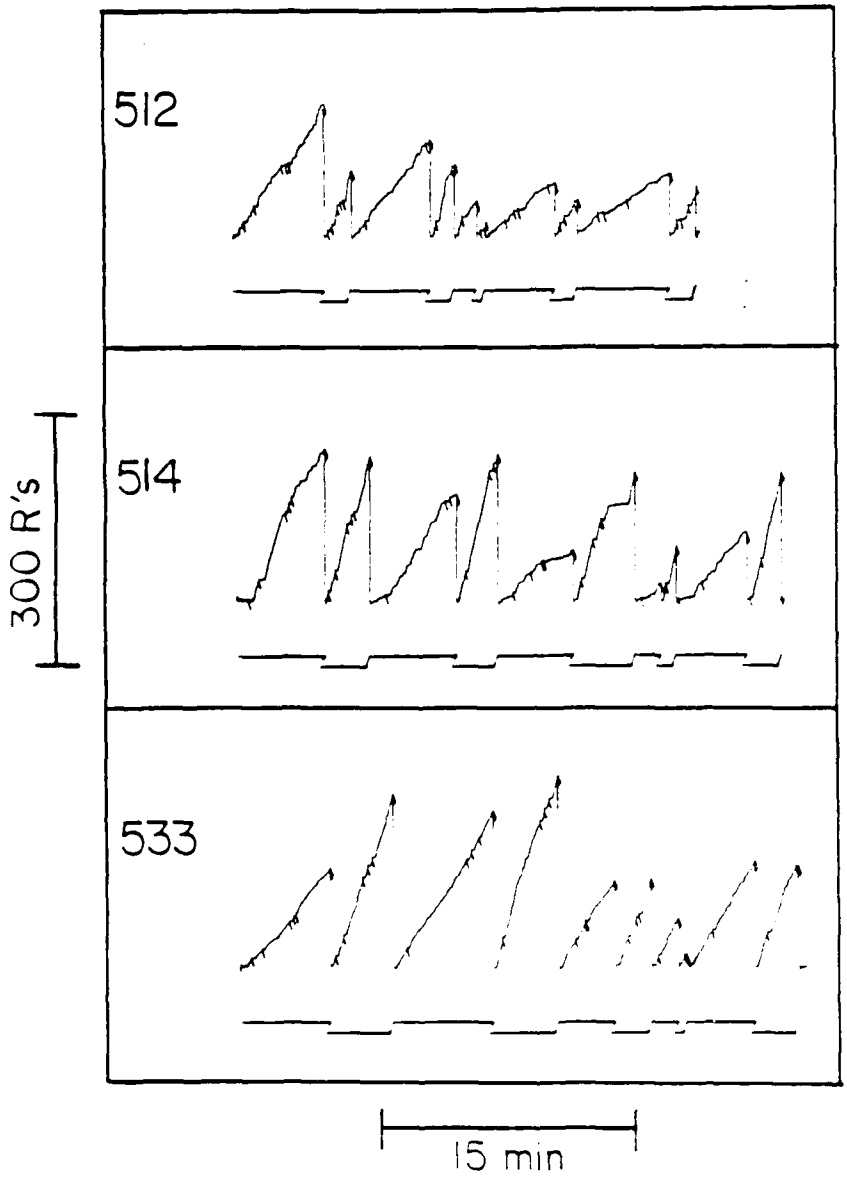

Figure 14. Cumulative records of responding under the multiple VI-VR schedule. The number of responses per reinforcer was approximately matched. Event pen down: VR component. Event pen up: VI component. Hatch marks indicate food delivery.

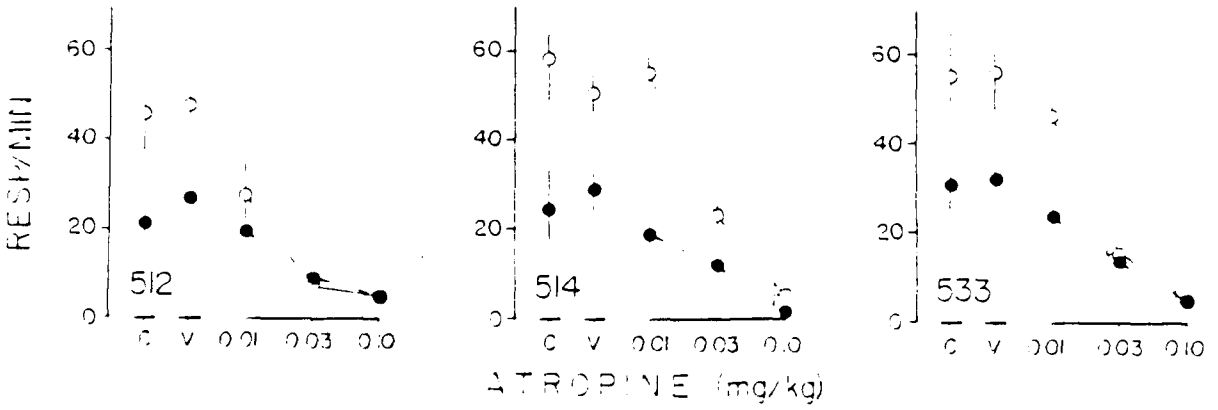

Figure 15. Effects of atropine on responding under the multiple VI-VR schedule. The number of responses per reinforcer was approximately matched. Open circles: rate during VI. Filled circles: rate during VR. Points above C show means from control sessions that immediately preceded injections and those above V show effects of vehicle (water) injection. Bars display ranges. Where bars are not visible, the point covers the range. All doses were administered at least twice.

Figure 16 shows the effects of atropine when combined with physostigmine (0.04 mg/kg for Subjects 512 and 514; 0.08 mg/kg for Subject 533). For Subjects 512 and 533, physostigmine alone reduced response rates, and none of the doses of atropine tested antagonized that effect. For Subject 514, physostigmine did not change the dose effects of atropine appreciably (compare to Fig. 15). For none of the three subjects was there any indication that effects were reinforcement-schedule dependent.

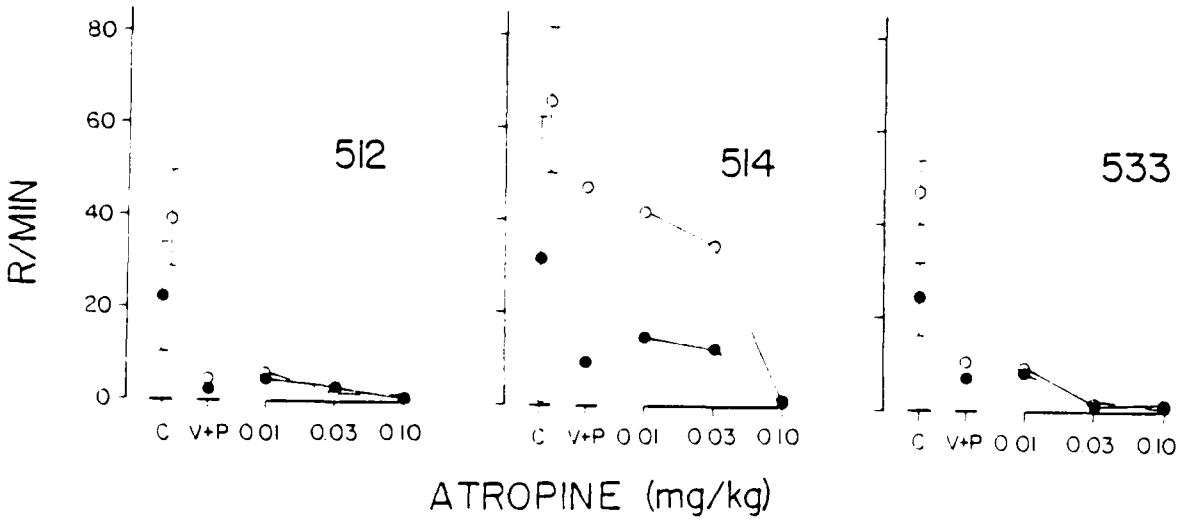

Figure 16. Effects of atropine in combination with physostigmine. Open circles show response rates during the VR schedule and filled circles show rates during the VI schedule. Points above C are means from sessions that immediately preceded those in which drugs were administered; the bars show the 95% confidence limits. All other points are means of two determinations. Points above V+P show effects of physostigmine when given in combination with an injection of distilled water. The dose of physostigmine was 0.04 mg/kg for Subjects 512 and 514 and 0.08 mg/kg for Subject 533.

Post-session dosing with atropine continued for 61, 73, and 66 sessions for Monkeys 512, 514, and 533, respectively. Comparison of Figure 17 with Figure 15 reveals that the effects of atropine were little affected by administering 0.1 mg/kg of the drug after each session. Monkey 514's response rate during the VR schedule was a bit more sensitive to the rate-reducing effect of the smallest dose, but other than that no changes were evident.

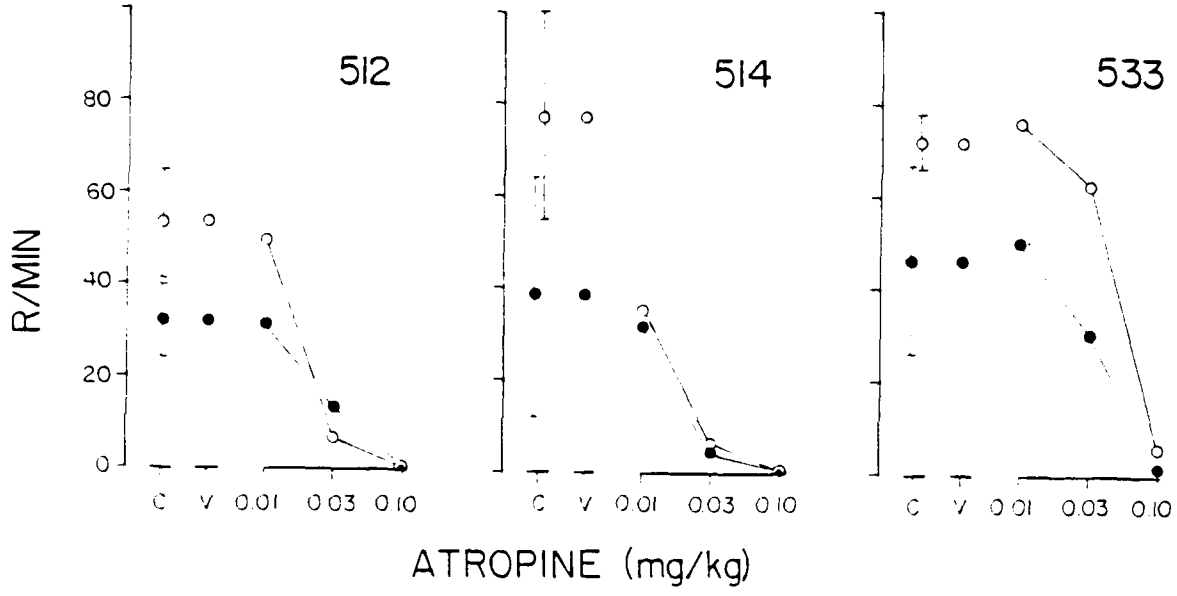

Figure 17. Effects of atropine when each session was followed by an injection of 0.1 mg/kg of the drug. Open circles show rates during the VR schedule and filled circles show rates during the VI schedule. Points above C are means from sessions that preceded those in which pre-session drug injections occurred; the bars show the 95% confidence interval. All other points are means of two determinations. Points above V show effects of administering the vehicle (distilled water) before sessions.

Certainly, nothing akin to tolerance was seen. Similarly, repeated post-session administration of atropine did not result in any consistent alteration of the interaction between physostigmine and atropine. During this phase atropine still did not act as an effective antagonist of physostigmine. This is illustrated in Fig. 18, which shows the effects of combinations of atropine and physostigmine. Repeated post-session dosing did not produce consistent changes in the effects of physostigmine alone. Its effects were greater for Subject 533, less for Subject 512, and about the same for Subject 514 (cf. Fig. 16).

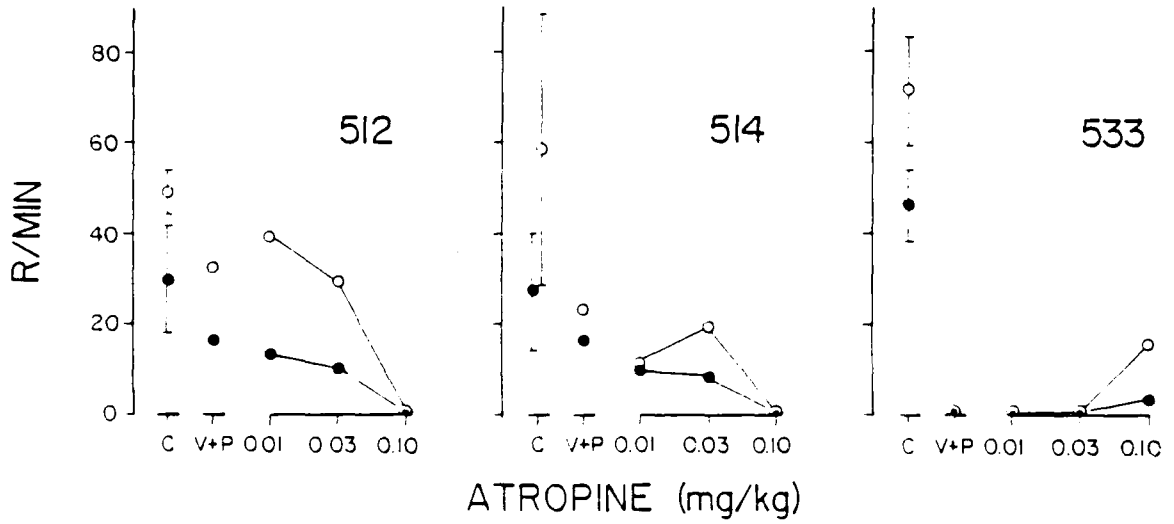

Figure 18. Effects of combinations of atropine and physostigmine when each session was followed by an injection of atropine (0.1 mg/kg). Open circles show rates during the VR schedule and filled circles show rates during the VI schedule. Points above C show means from sessions that preceded those in which drug combinations were tested; bars show the 95% confidence limits. All other points are means of two determinations. Points above V+P show effects of physostigmine (0.04 mg/kg for Subjects 512 and 514; 0.08 mg/kg for Subject 533) when it was given with an injection of the vehicle (distilled water).

Fig. 19 illustrates dose effects for atropine during the phase where atropine (0.1 mg/kg) was administered before each session. This phase lasted for 65, 57, and 38 sessions for Subjects 512, 514, and 533, respectively. For two of the subjects, pre-session drugging produced profound changes in performance. Subject 533's data are not comparable (even though they are presented) because this animal had to be treated differently from the other two. Specifically, Monkey 533 became ill at the end of the post-session dosing phase and had to be removed from the study for more than a month. Consequently, its exposure to pre-session drugging followed a drug-free period. For the other two monkeys, pre-session dosing resulted in a generalized suppression of responding. As the figure indicates, responding was considerably suppressed even when injections of the drug vehicle (distilled water) preceded sessions. In fact, reponding remained suppressed for several sessions after repeated drugging was halted. Because of this generalized suppression, interactions between physostigmine and atropine were not assessed.

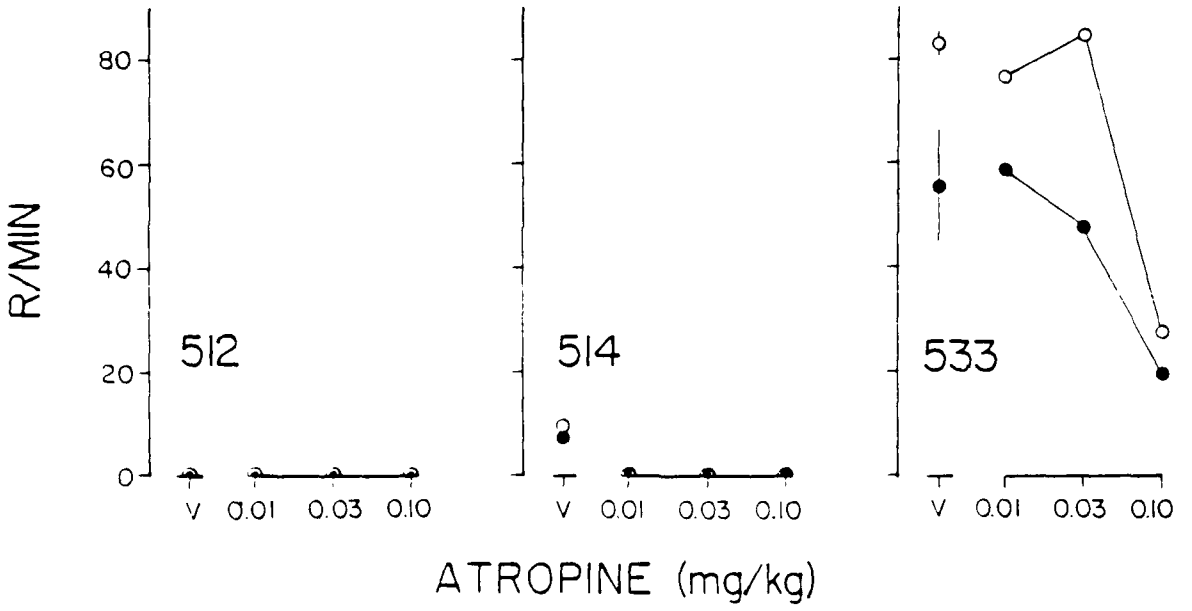

Figure 19. Effects of atropine during repeated pre-session injections of the drug (0.1 mg/kg). All points are means of two determinations, and the bars on the points above V are ranges. Open circles show rates under the VR schedule and filled circles show rates under the VI schedule. Points above V show effects of injecting only distilled water before sessions.

Procedure 4: Performance under interval and ratio schedules of food presentation in which temporal frequency of food presentation was equated. Procedure 4 may be viewed as a companion to Procedure 3. In Procedure 3 the two components of the multiple schedule were equated with respect to number of lever presses per food presentation and differed with respect to the type of schedule. In Procedure 4 the same two types of schedules were used but they were equated for temporal distribution of food presentations. Again, a two-component multiple schedule was used, but in this case the VI schedule initially was "yoked" to the VR schedule. Specifically, when the VR schedule of food presentation was in effect, times between successive food presentations were recorded. These times were then used in the VI component of the multiple schedule. That is, the VI's were "yoked" to the inter-food-presentation intervals in the VR component. As in Procedure 3, components alternated after two to seven food presentations, and sessions included five of each type of component. As in the previous study, direct yoking was discontinued once stable performance had been established. The behavior of only two of the three monkeys exposed to this procedure came under control. The third monkey developed very low rates of responding under the VR schedule and was exposed unsuccessfully to alternative procedures in an attempt to generate schedule-appropriate patterning. For the remaining two monkeys, VR values of 33 and 45 were used. Time limits were set for each component so that exposure to both occurred even if responding was suppressed totally in one or the other. The time limit was set at 200% of the average time to complete the component under control (non-drug) conditions. The numbers of sessions required to establish stable responding were 160 for Monkey 528 and 143 for Monkey 536.

As in Procedure 3, this procedure allowed for a within-subject comparison of drug effects on VI and VR responding. In this case, however, baseline frequency and temporal distribution of food presentation were equated in the two components. Thus, Procedures 3 and 4 allowed assessment of the role of schedule type under conditions in which reinforcement frequency (Procedure 4) or reinforcement probability (Procedure 3) was equated.

Cumulative records of control performance for the two monkeys who were exposed to drugs are shown in Figure 20. Although the VR schedule controlled a higher average rate than the VI in all control sessions, the differences were not large.

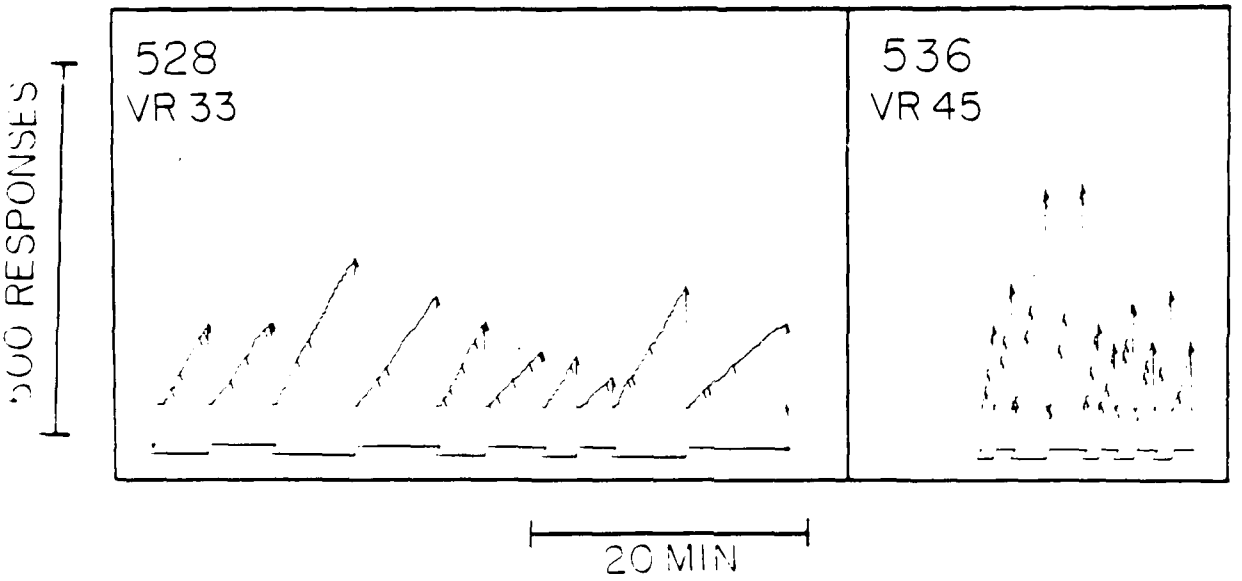

Figure 20. Cumulative response records of responding under the multiple VR yoked VI schedule. Y-axis: cumulative responses. X-axis: time. The event pen was deflected downward during the VR schedule. Hatch marks indicate food deliveries.

Dose-effect curves for atropine were determined for two subjects, and are shown in Figure 21. Once again, only decreases were observed, and as in Procedure 3, the effective dose range for this performance is an order of magnitude lower than that for performance under Procedures 1 and 2.

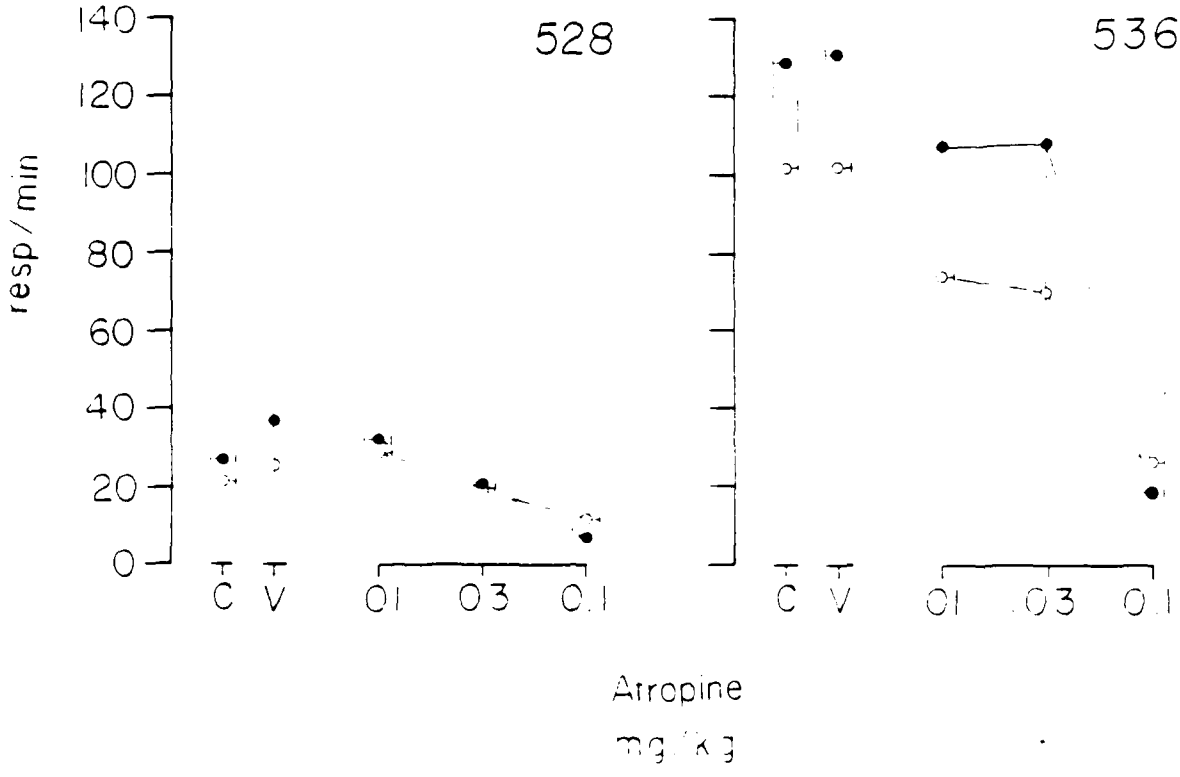

Figure 21. Dose-effect curves for monkeys under the multiple VR-VI schedule. The inter-reinforcement times were approximately matched. Filled circles indicate the mean number of responses per minute during the VR component for control days (points above C), vehicle injections (points above V) and three doses of atropine. Open circles indicate the mean number of responses per minute during the VI component. Bars indicate ranges.

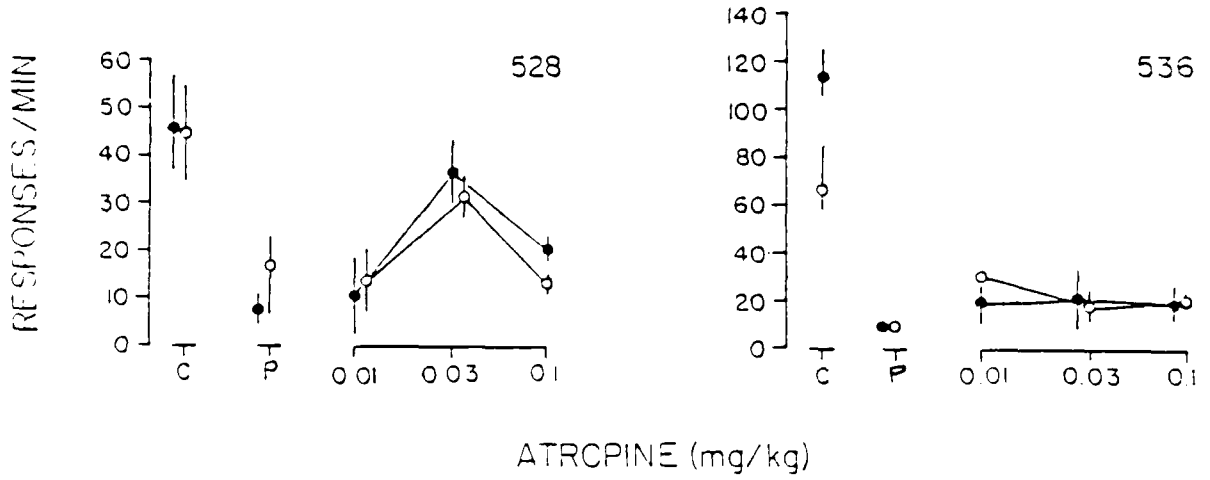

Figure 22. Effects of atropine when combined with physostigmine under conditions of acute administration. Filled circles show response rates during the VR schedule and open circles display those under the VI schedule. Points above C show means and ranges of control (non-drug) values. Points above V show effects of injecting the atropine vehicle in combination with physostigmine. Doses of physostigmine were 0.0[illegible] mg/kg for Monkey 528 and 0.08 mg/kg for Monkey 536.

Figure 22 illustrates effects of combinations of physostigmine (0.05 mg/kg for Subject 528 and 0.08 mg/kg for Subject 536) with a range of doses of atropine under conditions of acute administration. For Monkey 528, atropine antagonized response-rate decreases produced by physostigmine in both components of the multiple schedule. For Subject 536, in contrast, little antagonism was seen.

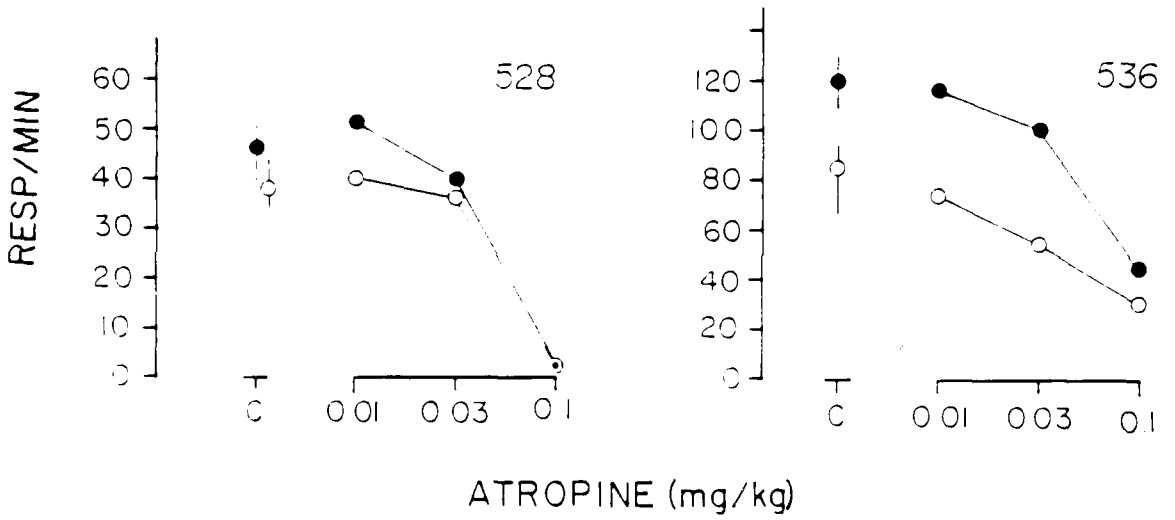

Figure 23. Effects of atropine during repeated post-session administration of 0.1 mg/kg of atropine. Details are the same as those in Figure 22.

Shown in Figure 23 are effects of atropine during repeated post-session administration of 0.1 mg/kg of atropine. Comparison of these results to those displayed in Figure 21 shows that repeated post-session dosing did not produce significant changes in atropine's effects.

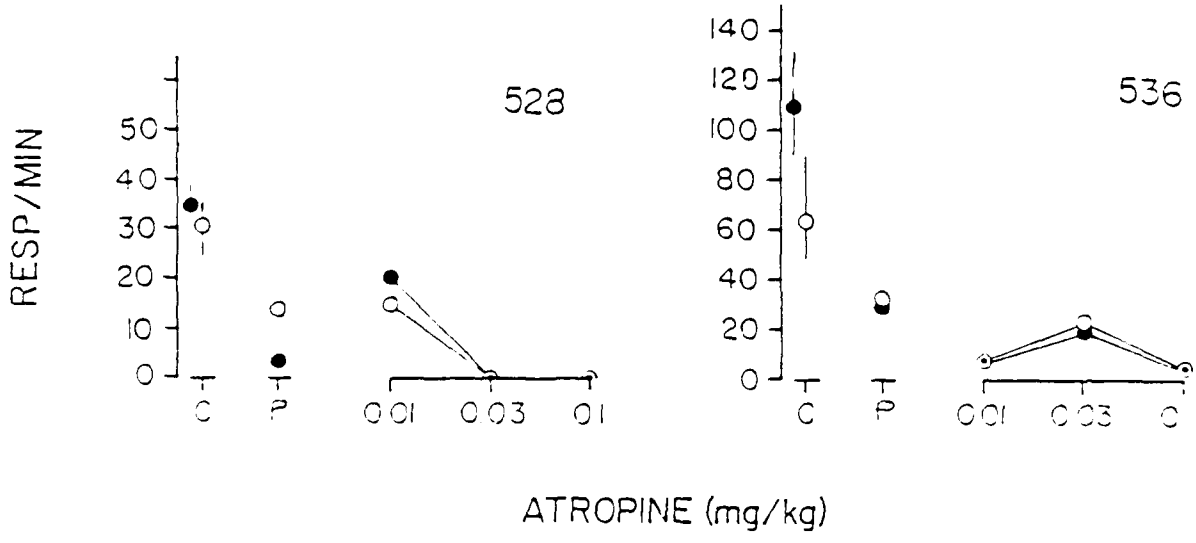

Figure 24. Effects of atropine in combination with physostigmine during repeated post-session administration of atropine. Details are the same as for Figure 22.

Repeated post-session dosing with atropine, however, was followed by a change in the nature of the interaction of atropine and physostigmine for Monkey 528. This is illustrated in Figure 24. During the post-session regimen, atropine no longer served to antagonize the rate-decreasing effects of physostigmine. The interaction between physostigmine and atropine was not changed during repeated post-session dosing for Subject 536.

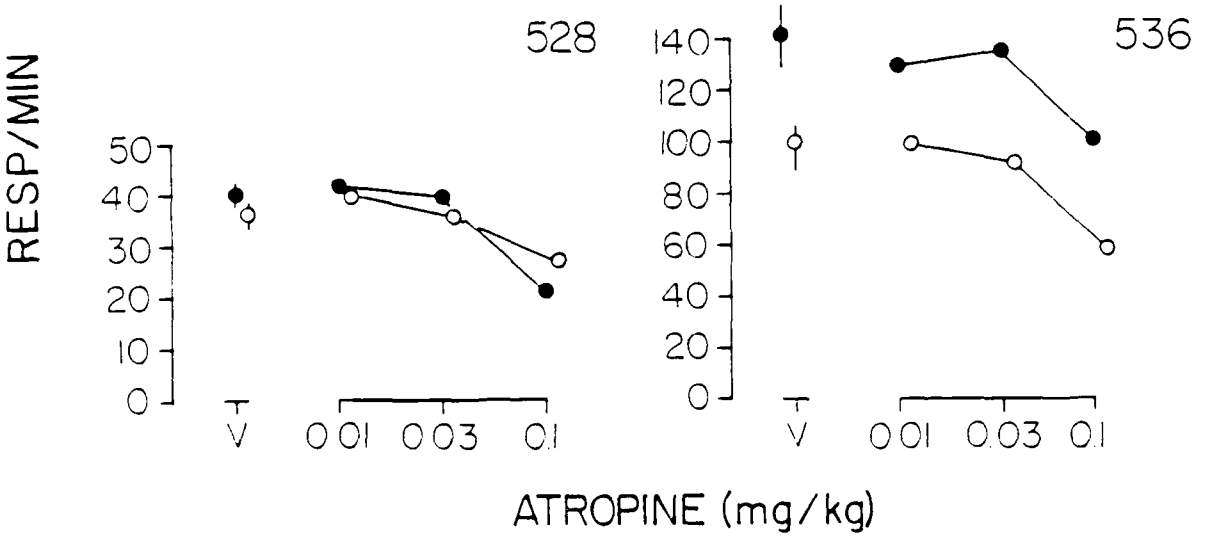

Figure 25. Effects of atropine during repeated pre-session administration of 0.1 mg/kg. Details are like those in Figure 22.

In contrast to effects of repeated post-session injections of atropine, repeated pre-session injection of the drug was followed by the development of tolerance to the rate-decreasing effects of the drug. These changes can be seen by comparing the data in Figure 21 with those in Figure 25. Decreases produced by 0.1 mg/kg of atropine were substantially attenuated during the chronic pre-session drugging phase, especially for Monkey 536. It is interesting that the effects of physostigmine were restored in Subject 528 during the repeated pre-session drugging phase as shown in Figure 26.

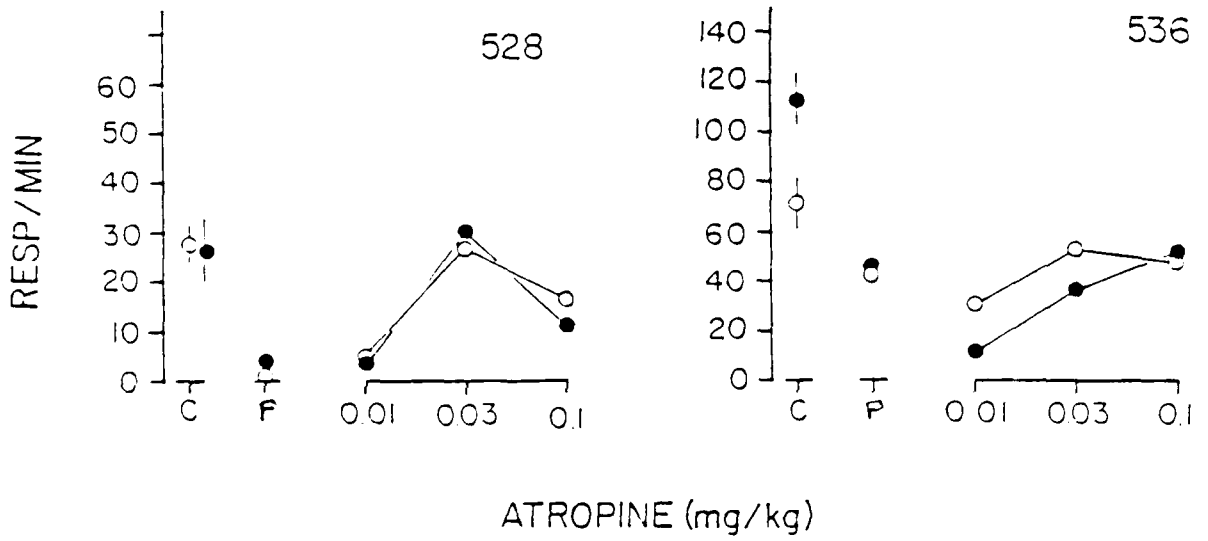

Figure 26. Effects of atropine in combination with physostigmine during repeated pre-session administration of atropine. Details are the same as those in Figure 22.

The nature of the drug interaction, however, was little changed for Subject 536. Thus for these two subjects, repeated pre-session administration of atropine led to the development of tolerance to atropine's effects but did not result in a significant change in the nature of the drug's interaction when compared to that observed under acute conditions (cf. Figure 22).

Conclusions

Conclusions that may be drawn on the basis of the studies completed are largely tentative owing to the considerable inter- and intra-subject variability that was encountered. One conclusion that is not tentative, however, is that the effects of atropine, both acute and chronic, were quite variable both within and across subjects. This finding implies that even the highly rigorous conditions employed here were not enough to prevent other, unknown variables from exerting effects. Whether these variables have to do with environmental or genetic influences is not known at this time, but some of the tentative conclusions that are outlined below suggest that environmental factors are the likely culprits.

With regard to the major purposes of the experiments as outlined in the introduction, a few general conclusions may be reached. First, there was very little evidence that the type of reinforcement schedule or the type of motivation was an important determinant of the nature of atropine's effects. Acutely, atropine generally produced dose-related decreases in response rates, and these decreases occurred about equally in both components of each of the multiple schedules studied. The only hint that a schedule-related difference can be observed was found in the data for the monkeys exposed to Procedure 2, in which fixed-ratio schedules of avoidance of electric shock and food presentation were compared. Following repeated atropine administration, some tolerance was observed in the component in which food presentation maintained responding but not in the component in which responding terminated a stimulus associated with the delivery of shock. This finding should be interpreted with caution, however, because it appeared that responding in the component with food presentation was influenced by the presence of the shock avoidance schedule in the other component. Specifically, food-reinforced responding was maintained well under circumstances in which none of the earned food pellets were consumed.

A second major aim of the project was to determine whether there would be any consistent differences in effects of repeated pre-session versus repeated post-session administration of atropine. Here, too, not much of the evidence is consistent with the view that such a change in procedure makes an important difference in the behavioral effects of atropine. Only in Procedure 4 where VI and VR schedules were compared did results appear as predicted. In this study, repeated pre-session atropine injections were followed by the development of tolerance whereas repeated post-session injections did not result in tolerance. This finding is especially perplexing in light of the results of Procedure 3 in which VI and VR schedules also were compared. In this set of experiments post-session atropine administration did not result in tolerance (as was the case for Procedure 4), but repeated pre-session administration not only did not lead to tolerance but instead resulted in a sensitization to the effects of atropine. It may be important to note, however, that the sensitization was more behavioral than pharmacological as indicated by the fact that pre-session drugging resulted in a generalized suppression of responding in the experimental apparatus that was evident even when the drug was not administered (including tests in which no injection at all preceded sessions).

One consistent finding in these experiments was that under both acute and repeated-administration conditions, employment of a negative

reinforcement contingency involving electric shock rendered behavior much more resistant to atropine's disruptive effects. That is, responding maintained solely by positive reinforcement was altered at doses an order of magnitude smaller than those needed to change responding under multiple schedules in which positive-reinforcement components alternated with components in which negative reinforcement was arranged. Whether this difference is due specifically to the use of electric shock and/or food as motivators can be resolved only by additional research.

An additional surprise in the data from these experiments was the finding that atropine and physostigmine did not consistently function as antagonists. Although it should be noted that previous research with schedule-controlled behavior of squirrel monkeys has resulted only in evidence "suggestive of antagonism" (4, p. 37) when atropine and physostigmine were administered concurrently. In Procedure 1, in which VI schedules of positive and negative reinforcemnt were compared, the two drugs interacted in an odd way to result in the only elevations in response rate seen during the studies, an interaction that is difficult to characterize as antagonism. In Procedure 3 it was also true that no antagonism was seen across the range of doses tested. By contrast, antagonism was seen in Procedures 2 and 4. The variables responsible for these disparate effects remain obscure. Obviously, a very thorough dose-response analysis in which doses of atropine and physostigmine both are varied across a wide range in a reasonable number of subjects will allow determination of the contribution of dose and constitutional factors in producing the variability seen in the present studies.

One important fact the results of these studies point out is that the effects of atropine on behavior and how the drug interacts with physostigmine are highly variable across individual monkeys. This finding indicates that subtle aspects of the environment and/or the constitution of the animals can modify greatly how atropine acts. To the extent that these findings have relevance for human behavior, they suggest that atropine's actions are too sensitive to an array of variables to result in consistent effects in a complex environment.

References

1. Goodman, L.S. and Gilman, A. (1975) The Pharmacological Basis of Therapeutics. New York: MacMillan.

2. Carlton, P.L. (1963) Cholinergic mechanisms in the control of behavior by the brain. Psychological Review, 70, 19-39.

3. Longo, V.G. (1966) Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacological Reviews, 18, 965-996.

4. Chait, L.D. and Balster, R.L. (1979) Effects of phencyclidine, atropine and physostigmine, alone and in combination, on variable-interval performance in the squirrel monkey. Pharmacology Biochemistry & Behavior, 11, 37-42.

5. McDonough, J.H. (1982) Effects of anticholinergic drugs on DRL performance of rhesus monkeys. Pharmacology Biochemistry & Behavior, 17, 85-90.

6. Mertens, H.W., Steen, J.A. and Lewis, M.F. (1976) Some behavioral effects of pesticides: The interaction of mevinphos and atropine in pigeons. Aviation Space and Environmental Medicine, 47, 137-141.

7. Kurtz, P.J. (1977) Behavioral and biochemical effects of the carbamate insecticide, mobam. Pharmacology Biochemistry & Behavior, 6, 303-310.

8. Leitenberg, H. (Ed.) (1976) Handbook of Behavior Modification and Behavior Therapy. Englewood Cliffs, NJ: Prentice Hall.

9. Johnston, J.M. (Ed.) (1975) Behavior Research and Technology in Higher Education. Springfield, IL: Thomas.

10. Bivens, L.W. and Ray, O.S. (1968) Amphetamine, atropine and meprobamate effects on operant behavior in the rat. Archives Internationale de Pharmacodynamie et Therapie, 172, 380-392.

11. Hines, G., Lee, A.E. and Miller, W.T. (1970) Effect of atropine dose on the suppression of water-reinforced VI responding. Psychonomic Science, 20, 37-38.

12. Willis, R.D. and Windland, L.M. (1968) Effects of repeated administration of atropine on two multiple schedules. Psychonomic Science, 13, 139-140.

13. Heise, G.A. amd Lilie, N.L. (1970) Effects of scopolamine, atropine and d-amphetamine on internal and external control of responding on non-reinforced trials. Psychopharmacologia, 18, 38-49.

14. McKearney, J.W. (1981) Individual differences in effects of tricyclic antidepressants and anticholinergic drugs on operant behavior in the squirrel monkey. Life Sciences, 28, 2049-2054.

15. Catania, A.C. (1979) Learning. Englewood Cliffs, NJ: Prentice Hall.

16. Skinner, B.F. (1953) Science and Human Behavior. New York: Free Press.

17. Barrett, J.E. (1976) Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. Journal of Pharmacology and Experimental Therapeutics, 196, 605-615.

18. Branch, M.N. (1979) Consequent events as determinants of drug effects on schedule-controlled behavior: modification of effects of cocaine and d-amphetamine following chronic amphetamine administration. Journal of Pharmacology and Experimental Therapeutics, 210, 354-360.

19. McKearney, J.W. (1974) Effects of d-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. Journal of Pharmacology and Experimental Therapeutics, 190, 141-153.

20. Herrnstein, R.J. (1958) Effects of scopolamine on a multiple schedule. Journal of the Experimental Analysis of Behavior, 1, 351-358.

21. Kelleher, R.T. and Morse, W.H. (1968) Determinants of the specificity of behavioral effects of drugs. Ergebnisse der Physiologie Biologischen Chemie und Experimentellen Pharmakologie, 60, 1-56.

22. Herman, Z.S. and Slominska-Zurek, J. (1979) Central cholinergic receptor supersensitivity after long-term atropine administration. Psychopharmacology, 64, 337-340.

23. Takeyasu, K., Uchida, S., Noguchi, Y., Fujita, N., Saito, K., Hata, F., and Yoshida, H. (1979) Changes in brain muscarinic acetylcholine receptors and behavioral responses to atropine and apomorphine in chronic atropine-treated rats. Life Sciences, 25, 585-592.

24. Hughes, R.N. (1982) A review of atropinic drug effects on exploratory choice behavior in laboratory rodents. Behavioral Neurology and Biology, 34,5-41.

25. Dews, P.B. (1978) Behavioral tolerance. In N. Krasnegor (Ed.) Behavioral tolerance. NIDA Research Monograph 18. Washington: DHEW. Pp. 18-26.

26. Chen, C.S. (1968) A study of the alcohol-tolerance effect and the introduction of a new behavioral technique. Psychopharmacologia, 12, 433-440.

27. Kalant, H., LeBlanc, A.E. and Gibbins, R.J. (1971) Tolerance and dependence on some non-opiate psychotropic drugs. Pharmacological

28. Campbell, J.C. and Seiden, L.S. (1973) Performance influence on the development of tolerance to amphetamine. Pharmacology Biochemistry and Behavior, 1, 703-708.

29. Carlton, P.L. and Wolgin, D.L. (1971) Contingent tolerance to anorexigenic effects of amphetamine. Physiology and Behavior, 7, 221-223.

30. Pearl, R.G. and Seiden, L.S. (1976) The existence of tolerance to and cross-tolerance between d-amphetamine and methylphenidate for their effects on milk consumption and differential-reinforcement-of-low-rate performance in the rat. Journal of pharmacology and Experimental Therapeutics, 198, 635-647.

31. LeBlanc, A.E., Gibbins, R.J. and Kalant, H. (1973) Behavioral augmentation of tolerance to ethanol in the rat. Psychopharmacologia, 30, 575-576.

32. Wenger, J.R., Tiffany, T.M., Bombardier, C., Nicholls, K. and Woods, S.C. (1981) Ethanol tolerance in the rat is learned. Science, 213, 575-576.

33. Murray, T.F., Craigmill, A.L. and Fischer, G.J. (1977) Pharmacological and behavioral components of tolerance to LSD and mescaline in rats. Pharmacology Biochemistry and Behavior, 7, 239-244.

34. Branch, M.N. (1983) Behavioral tolerance to stimulating effects of pentobarbital: a within-subject analysis. Pharmacology Biochemistry and Behavior, 18, 25-30.

35. Harris, R.A. and Snell, D. (1980) Effects of acute and chronic administration of phenobarbital and d-amphetamine on schedule-controlled behavior. Pharmacology Biochemistry and Behavior, 12, 47-52.

36. Tang, M. and Falk, J.L. (1978) Behavioral and pharmacological components of phenobarbital tolerance. In N. Krasnegor (Ed.) Behavioral tolerance. NIDA Research Monograph 18. Washington; DHEW. Pp. 142-148.

37. Woolverton, W.L., Kandel, D. and Schuster, C.R. (1978a) Tolerance and cross-tolerance to cocaine and d-amphetamine. Journal of Pharmacology and Experimental Therapeutics., 205, 525-535.

38. Woolverton W.L., Kandel, D. and Schuster, C.R. (1978b) Effects of repeated administration of cocaine on schedule-controlled behavior of rats. Pharmacology Biochemistry and Behavior, 9, 327-337.

39. Carder, B. and Olson, J. (1973) Learned behavioral tolerance to marihuana in rats. Pharmacology Biochemistry and Behavior, 1, 73-76.

40. Olson, J. and Carder, B. (1974) Behavioral tolerance to marihuana as a function of amount of prior training. Pharmacology Biochemistry and Behavior, 2, 243-247.

41. Sidman, M. (1960) Tactics of Scientific Research. New York: Basic Books.

42. Corfield-Sumner, P.K. and Stolerman, I.P. (1978) Behavioral tolerance. In D.E. Blackman & D.J. Sanger (Eds.) Contemporary Research in Behavioral Pharmacology, New York: Plenum. Pp. 391-448.

43. Schuster, C.R., Dockens, W.S. and Woods, J.H. (1966) Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia, 9, 170-182.

44. Snapper, A.G. and Inglis, G. (1978) The SKED Software System: Time-Shared SuperSKED. Kalamazoo, MI: State Systems.

45. deVilliers, P.A. (1974) Reinforcement and response rate interaction in multiple random interval-avoidance schedules. Journal of the Experimental Analysis of Behavior, 18, 499-507.

DISTRIBUTION LIST

1 copy — Commander
US Army Medical Research and Development Command
ATTN: SGRD-RMI-S
Fort Detrick, Frederick, Maryland 21701-5012

5 copies — Commander
US Army Medical Research and Development Command
ATTN: SGRD-PLE
Fort Detrick, Frederick, Maryland 21701-5012

2 copies — Defense Technical Information Center (DTIC)
ATTN: DTIC-DDAC
Cameron Station
Alexandria, VA 22304-6145

1 copy — Dean
School of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

1 copy — Commandant
Academy of Health Sciences, US Army
ATTN: AHS-CDM
Fort Sam Houston, TX 78234-6100